Section of Endocrinology

President H L Sheehan MD

Meeting January 25 1961

Discussion on the Diagnosis of Hyperparathyroidism [*Abridged*]

Professor C E Dent (*London*) opened the discussion on the diagnosis of hyperparathyroidism by giving a review of the experience gained at University College Hospital on 70 successfully operated patients, thus bringing up to date his earlier review on 40 patients (Dent 1959).

REFERENCE
Dent C E (1959) *Proc. R. Soc. Med.* **52**, 993

Dr R R McSwiney and Professor F T G Prunty (*London*)

The Diagnosis of Minimal Hyperparathyroidism – Determination of Theoretical Renal Phosphorus Threshold

It is our experience, like that of others, that many more patients having parathyroid adenomata present clinically with calcium-containing renal stones than with the clinical picture of hyperparathyroidism with skeletal involvement. The differentiation of these patients from others with renal calculi who do not have hyperparathyroidism is an important matter which may be difficult. They often show only minimal evidence of hypercalcæmia and further supportive evidence of the presence of hyperparathyroidism may be of the greatest value.

In this group of patients we have at present two criteria indicating the necessity for further investigation. The first is severe renal tract involvement with calculi or less commonly nephrocalcinosis, especially leading to complications such as renal failure or nephrectomy. The second is suspicion concerning possible abnormality of fasting serum calcium levels. Values between the upper 80 and 95% confidence limits are regarded as suspicious, those above the 95% level as definite hypercalcæmia.

Serum calcium values fluctuate from time to time in patients with hyperparathyroidism, so that hypercalcæmia may be present on some occasions but not on others. These patients do not exhibit hyperphosphatasia, which is often of value in the differentiation of hypercalcæmia, and it is found that determination of serum phosphorus values is of poor differential value (*see* Table 1). In half our patients with hyperparathyroidism definite hypercalcæmia did not consistently occur and in one patient this was not observed on any occasion. In this and 4 other patients elevation of ionized calcium was not found. A considerable number of patients with renal calculi had suspicious serum calcium levels. The two groups could not be differentiated by the level of the urine calcium on either normal calcium intakes or intakes reduced to 150 mg daily.

Most attention has been given to abnormalities of phosphate metabolism in finally confirming the diagnosis.

Determination of the theoretical renal phosphorus threshold (R.P.Thr.) has the advantage of

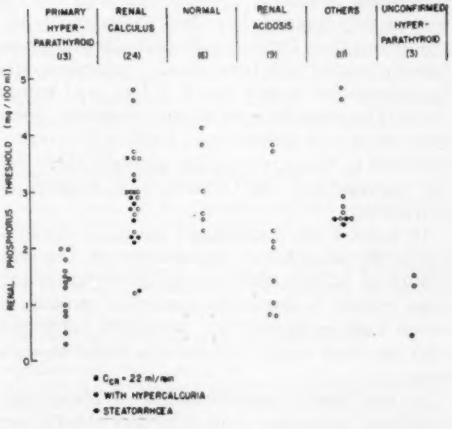

Fig 1 *Scatter diagram of results for theoretical renal phosphorus threshold*

being independent of the resting serum phosphorus level. It is carried out as previously described (Hyde *et al.* 1960). Results with this procedure are shown in Fig 1. In all 13 cases from which parathyroid tumours have now been removed R.P.Thr. was less than 2 mg/100 ml, and in 3 other patients who have not yet had operations for reasons of a non-technical nature. In 11 of these patients creatinine clearance exceeded 60 ml/min, in 2 it was 10 and 41 ml/min respectively.

Table 1
Abnormalities of phosphorus metabolism

	Plasma phosphorus			*Renal handling of phosphorus No. of abnormal patients*			
	Always normal	*Suspicious*	*Low*	*Cp/Ccr*	*P.E.I.*	*T.R.P.*	*R.P.Thr.*
All cases							
Hyperparathyroidism (23)	5	10	8	8 (10)	7 (10)	6 (10)	—
Renal calculi (44)	14	23	7	11 (34)	17 (34)	7 (34)	—
eshold cases							
yperparathyroidism (13)	2	5	6	8 (9)	7 (9)	6 (9)	13 (13)
Renal calculi (31)	11	13	7	8 (29)	8 (29)	6 (29)	*3 (19)

Note: Figures in brackets = number of patients tested
**see* text
Cp/Ccr = phosphate/creatinine clearance ratio
P.E.I. = phosphate excretion index
T.R.P. = tubular reabsorption of phosphate (%)
R.P. Thr. = renal phosphorus threshold

There are several patients with values of R.P.Thr. below 2 mg/100 ml who were not surgically explored on the grounds that there was evidence of an alternative cause for the low threshold. Thus 2 patients, R.P.Thr. 0·7 and 2·0 mg/100 ml, with renal calculi, had renal failure (creatinine clearance 22 and 28 ml/min) and the former may possibly have had secondary hyperparathyroidism. Patients with a tubular phosphate leak associated with renal tubular acidosis would be expected to show a low R.P.Thr., and indeed do so. The miscellaneous groups contained, apart from those with steatorrhœa, patients for control purposes in whom, on clinical grounds, there was no question of the presence of hyperparathyroidism.

In Table 1 are summarized results of abnormalities of phosphorus metabolism in the two groups of patients with hyperparathyroidism and renal calculi. It shows the number of patients in which each parameter was abnormal compared with the total number of patients tested in each case.

In our hands determinations of phosphate/creatinine clearance ratio (Cp/Ccr) (McGeown 1957), phosphate excretion index (P.E.I.) (Nordin & Fraser 1960) and percentage tubular reabsorption of phosphate (T.R.P.) (Thomas *et al.* 1958) were all less reliable than the R.P.Thr. in the patients with hyperparathyroidism who were operated upon. They also show a number of false positive results in patients with renal calculi who were not considered to have hyperparathyroidism by other criteria or did not have renal tubular acidosis or significant depression of the glomerular filtration rate.

The determination of the maximal tubular reabsorption of phosphate (Tmp) (Thompson & Hiatt 1957) has not seemed useful since it is difficult to obtain constant values at varying levels of serum phosphorus.

The R.P.Thr. always returns to normal in ten to fourteen days after parathyroidectomy. In 4 of 6 instances this has not been the case with the P.E.I.

We conclude that the most valuable parameter of abnormal phosphate excretion is the R.P.Thr. In every patient in whom this has been used as an adjunct to the diagnosis of hyperparathyroidism an adenoma has been found, but it can scarcely be expected that in future every patient will be found to have this abnormality. Care must be taken in differentiating patients with renal tubular defects or secondary hyperparathyroidism.

We would like to thank Mr J M Pullan who removed most of the parathyroid tumours, and all those who assisted in the technical investigations.

REFERENCES

Hyde R D, Vaughan Jones R, McSwiney R R & Prunty F T G (1960) *Lancet* i, 250
McGeown M G (1957) *Clin. Sci.* **16**, 297
Nordin B E C & Fraser R (1960) *Lancet* i, 947
Thomas W C, Connor T B & Morgan H G (1958) *J. Lab. clin. Med.* **52**, 11
Thompson D D & Hiatt H H (1957) *J. clin. Invest.* **36**, 550

Dr B E C Nordin (*Glasgow*)

Diagnosis of Primary Hyperparathyroidism

Our screening procedure for the diagnosis of primary hyperparathyroidism starts with the collection of a sample of urine covering a period of about two hours and a sample of blood taken at or near the midpoint of the urine collection. Calcium, phosphorus and creatinine are estimated in blood and urine. This procedure is equally applicable to in-patients and out-patients and reveals not only the plasma calcium and phosphate concentrations but also the urinary calcium/creatinine ratio and the phosphate/creatinine clearance ratio from which the phosphate excretion index can be calculated.

Plasma calcium: The crucial importance of plasma calcium in the diagnosis cannot be overemphasized but has been dealt with by many other writers. Most workers believe that total calcium varies directly with ionic calcium in primary hyperparathyroidism, but if recent claims to the contrary (Lloyd & Rose 1958, Freeman & Breen 1960) are confirmed the measurement of ultrafiltrable calcium will become indispensable; this is most easily performed by ultracentrifugation (Loken *et al.* 1960). The measurement of ionic calcium (Rose 1957) is of the greatest interest and importance in research but is probably unnecessary in clinical practice because its value is so close to that of the ultrafiltrable fraction. There is an increasing tendency to diagnose primary hyperparathyroidism on plasma calcium values which are at the edge of normality (McGeown & Morrison 1959). The justification for operation in such cases depends upon the subsequent clinical course. A recent report shows a reduction in the incidence of stones but not the complete elimination of stone formation which might have been expected (McGeown 1961).

Urinary calcium: The normal calcium/creatinine ratio in random samples of urine ranges from 0·03 to 0·28 (Nordin 1959). The absolute range is the same in twenty-four-hour collections on an average diet but the twenty-four-hour ratio is more reliable and more reproducible. About half our patients with primary hyperparathyroidism do not have hypercalciuria, possibly because at any given level of plasma calcium the parathyroid hormone tends to reduce calcium clearance (Kleeman *et al.* 1960). The urinary calcium/creatinine ratio shows some correlation with plasma calcium and is only significantly raised when the plasma calcium is high (Nordin 1961*a*). It is clear that stone formation in primary hyperparathyroidism is not solely due to hypercalciuria but may reflect the effect of the hormone upon urine pH (Nordin 1960, Fourman *et al.* 1960).

Plasma and urinary phosphate: Urinary phosphorus normally rises and falls with the concentration of phosphorus in the plasma and the relationship between them has been established by Nordin & Fraser (1960). The phosphate/creatinine clearance ratio (Cp/Ccr) can be calculated from the blood and urine samples as follows:

$$\frac{Cp}{Ccr} = \frac{\text{urine P} \times \text{plasma Cr}}{\text{plasma P} \times \text{urine Cr}}$$

The normal value can be predicted as follows:

$$\text{Normal Cp/Ccr} = 0{\cdot}055 \times \text{Plasma P} - 0{\cdot}07$$

The extent to which the observed value departs from the normal value is called the phosphate excretion index (P.E.I.) the normal range of which is −0·09 to +0·09. The P.E.I. correlates with the plasma calcium concentration (Nordin 1961*b*) and is a much more reliable index of relative hyperphosphaturia than the phosphate clearance or the tubular reabsorption of phosphate (Nordin 1961*b*). We have only encountered one normal P.E.I. in proven hyperparathyroidism; such cases undoubtedly occur and conversely high values are sometimes seen in so-called idiopathic hypercalciuria (Harrison 1960). This raises the question of what the relationship is between this condition and hyperparathyroidism.

Other procedures: We have found that phosphate excretion is not suppressed by calcium infusion in primary hyperparathyroidism (Nordin 1961*a*, *b*). Other possible tests in primary hyperparathyroidism include X-rays of the skeleton (Barnett & Nordin 1960), iliac crest biopsy which may show osteoporosis or osteitis fibrosa (Beck & Nordin 1960), the concentrating power of the kidney (Hellström *et al.* 1958) and the acidifying power (Fourman *et al.* 1960). The diagnostic value of these procedures is not yet known.

REFERENCES

Barnett E & Nordin B E C (1960) *Clin. Radiol.* **11**, 166
Beck J S & Nordin B E C (1960) *J. Path. Bact.* **80**, 391
Fourman P, Smith J W G & McConkey B (1960) *Lancet* i, 619
Freeman S & Breen M (1960) *Clin. Ortho.* No. **17**, 186
Harrison A R (1960) *Brit. J. Urol.* **32**, 383
Hellström J, Birke G & Edvall C A (1958) *Brit. J. Urol.* **30**, 13
Kleeman C R, Bernstein D, Rockney R, Dowling J P & Maxwell M H (1960) *In:* Proceedings of the Symposium on the Parathyroid Hormone, Houston, Texas (in press)
Lloyd H M & Rose G A (1958) *Lancet* ii, 1258
Loken H F, Havel R J, Gordan G S & Whittington S L (1960) *J. biol. Chem.* **235**, 3654
McGeown M G (1961) *Lancet* i, 586
McGeown M G & Morrison E (1959) *Postgrad. med. J.* **35**, 330
Nordin B E C
(1959) *Lancet* ii, 386
(1960) *Clin. Sci.* **13**, 477
(1961*a*) *Postgrad. Med.* **29**, 65
(1961*b*) *Adv. clin. Chem.* (in press)
Nordin B E.C & Fraser R (1960) *Lancet* i, 947
Rose G A (1957) *Clin. Chim. Acta* **2**, 227

Dr Mary G McGeown (*Belfast*)

The Value of the Calcium Infusion Test, Tests of Renal Tubular Function and Changes in the Serum Proteins in the Diagnosis of Hyperparathyroidism

Hyperparathyroidism is present in about 20% of patients with renal stones, but it is difficult to diagnose in these patients because the elevation of the serum calcium may be slight and tends to fluctuate. Various tests of parathyroid function have been devised, but there has been little information about their value in the diagnosis of hyperparathyroidism. Measurements of the proportion of the filtered phosphate reabsorbed by the renal tubules have proved disappointing as there are many false positives to these tests in patients with renal calculi and other types of hypercalcæmia, while in a considerable number of patients with hyperparathyroidism the phosphate clearance is normal (McGeown 1957, Morgan *et al.* 1960, McGeown & Field 1960). Results obtained with other tests of parathyroid function are considered.

The calcium infusion test: For three days before the infusion the patients ate a standard diet containing 150 mg calcium and 300 mg phosphate. Urine was collected in four-hour periods for the twenty-four hours before, and after the infusion. The infusion consisted of 15 mg of calcium per kg body weight, given as the gluconate, diluted in 400 ml of 5% dextrose, over a period of four hours, beginning at 10 a.m. Comparison of phosphate excretion with a control day is necessary because of diurnal variations in urinary phosphate.

Table 1 shows the changes in serum phosphorus and urinary phosphorus after calcium infusion. Patients with hyperparathyroidism are reported to have a lesser rise in serum phosphorus than normal subjects, usually less than 1·0 mg% (Howard *et al.* 1953). Six of the 16 hyperparathyroid patients had a rise of more than 1·5 mg% while in 5 it was less than 1·0 mg%, the remainder being intermediate. On the other hand there were 2 apparently euparathyroid subjects with renal stones who showed a rise of less than 1·0 mg%.

Patients with hyperparathyroidism are said to show a rise in urinary phosphate, or only a slight fall, following calcium infusion (Howard *et al.* 1953). Only 2 of the hyperparathyroid subjects behaved in this way, while 6 had a fall of more than 40%. Three of the 9 euparathyroid subjects with renal stones showed 'the hyperparathyroid' response.

Three of these patients had hyperparathyroid bone disease. In 2 of them the infusion of calcium scarcely changed the serum calcium while the serum phosphorus fell. The urinary phosphate decreased in all 3 patients.

Tests of renal tubular function: Hyperparathyroid subjects have been reported to show defects of renal tubular function (Fourman *et al.* 1960). Four hyperparathyroid subjects were studied and all were able to achieve a urine concentration at least in the lower normal range after water deprivation for eighteen hours. One produced a very concentrated urine (1,060 m.Osm/1.). When mannitol was infused the minimum concentration of the urine was well above that of plasma in all 4 patients, and the T^cH_2O was normal or just below normal (+4·0 to +6·8; normal +5 to +7 ml/min.) (McGeown 1961).

The ability to excrete an acid urine after loading with ammonium chloride was also studied. The dose of ammonium chloride was 0·1 g/kg body weight. Ten out of 11 hyperparathyroid patients produced a urine of pH 5·4 or lower, similar to normal subjects (McGeown 1961).

Table 1

Changes in serum phosphorus and in urinary phosphorus following calcium infusion

		Hyperparathyroid subjects ●	*Euparathyroid subjects with renal stones*
Fall in serum P		2	0
Increase in serum P (mg%)	<1·0	3	2
	1·0–1·5	5	2
	>1·5	6	5
Urine P (% change ■)	Increased	1	1
	Decreased <10	1	2
	Decreased 10–40	7	2
	Decreased >40	6	4

● Three with bone disease, 2 with renal stones, 1 asymptomatic

■ $\frac{\text{Change}}{\text{Control 24-hour excretion}} \times 100$

Changes in the serum proteins: Electrophoresis in barbitone buffer at pH 8·6 was carried out on 28 patients with hyperparathyroidism. In 14 no abnormalities of globulin pattern were present, while the remainder showed a variety of patterns, amongst which the specific pattern reported by Gordan (1960) (rise in α_2 and β globulins) did not occur. No electrophoretic pattern emerged which appeared to be associated with hyperparathyroidism.

These three tests of parathyroid function appear to be abnormal in relatively few patients with hyperparathyroidism. They may give misleadingly abnormal results in patients with renal calculi, where the greatest difficulties in making the diagnosis are encountered, also in patients with other types of hypercalcæmia. In view of these difficulties in interpreting the results they have no place in the clinical diagnosis of hyperparathyroidism. The time devoted to them would be

better used for the estimation of the serum calcium several times in every patient with calcareous renal stones.

Discussion: It may be difficult to distinguish the milk alkali syndrome from primary hyperparathyroidism, as many hyperparathyroid patients have peptic ulcers and have been taking milk and alkali for long periods. The two diseases may resemble each other closely in their biochemical features, including the response of the hypercalcæmia to cortisone. I have investigated 5 patients with peptic ulcers, hypercalcæmia and azotæmia. Three of them were found to have parathyroid adenomata when their necks were explored. One has had his neck explored without a parathyroid adenoma being found, but is still thought to have hyperparathyroidism because the exploration was followed by an abrupt but transient drop in serum calcium and blood urea levels. The fifth patient had a negative exploration and the hypercalcæmia gradually fell over the following six months, but reappeared when he went back to a diet containing milk. Milk alkali syndrome appears to be very rare in comparison with hyperparathyroidism.

The low serum phosphorus occurring in some patients with steatorrhœa is usually explained as being due to secondary hyperparathyroidism. I have had a patient of this type who had a serum calcium of 4·5 mg% and a serum phosphorus of 1·7 mg%. This patient came to autopsy and despite careful search no parathyroid tissue was found. This does not entirely exclude parathyroid hyperplasia but makes it unlikely, and suggests the possibility that there is some other explanation for the hypophosphatæmia in these patients.

REFERENCES
Fourman P, McConkey B & Smith J W G (1960) *Lancet* i, 619
Gordan G S (1960) *Acta endocr. Copenhagen*, Suppl. 51, 463
Howard J E, Hopkins T R & Connor T B (1953) *J. clin. endocrinol.* 13, 1
McGeown M G (1957) *Clin. Sci.* 16, 297
(1961) *Proc. Ass. Clin. Biochem.* 1, 46
McGeown M G & Field C M B (1960) *Lancet* ii, 1268
Morgan H G, Stewart W K & Grieve J (1960) *J. clin. Path.* 13, 494

Mr G L Fordyce (*Northwood, Middlesex*) pointed out that the initial sign of hyperparathyroidism was occasionally found in the mouth in the form of an epulis which might grow with extreme rapidity, simulating a sarcomatous lesion. He described briefly 3 cases of this type.

Dr Oliver Garrod (*London*) asked if there was any correlation between the severity of the patients' symptoms and the level of serum calcium.

Professor C E Dent, in reply to this question, said that he thought there was very little, but that each patient had a very exact threshold for symptoms.

Mr W M Keynes (*London*) asked if there was any method of distinguishing, before operation, between parathyroid hyperplasia and tumour.

Professor Dent replied that there was not.

There followed some discussion as to the existence of two separate parathyroid hormones, to which **Professor Dent** contributed in particular. He thought that it was well proved now that the same hormone was responsible for calcium-raising power and for the renal phosphate excretion. However, he believed that there might be a still undiscovered hormone responsible for producing osteitis fibrosa generalisata.

Meeting March 22 1961

Growth Hormone Assays in Human Serum

by Barbara J Boucher MB and
A Stuart Mason MD MRCP (*London*)

This paper describes some results obtained using the immunological assay for growth hormone (GH) in human serum described by Read & Stone (1958) and Read (1960). The results shown are averages of 3 assays done on separate days

Immunological Assay of Pituitary Hormones

and the variation has usually lain well within 50 µg each side of the mean.

The assay values in 19 normal subjects, apart from one low value, were found to lie between 100 and 480 µg/l. The mean of the group is 257 (S.D. =137). A few subjects have been studied over periods of time from two days to one year as shown in Fig 1 and no variation has been found. There is no difference between fasting and non-fasting GH levels.

A B	480^F			480^F	480^F						
R D C	120^F	120	120			120	120	120	120	120	
M H	120	120	120	120^F		120^F					
A J	240^F			240^F	240^F						
L R	80	80	80	80^F							
M R	180^F	180	180	180^F							
F S	220^F	220	220	220^F							
	am	1 pm	noct DAYS	2	3	2	3	4	11	12	MONTHS

Fig 1 *Variation of assay with time. F=fasting*

Twenty-nine acromegalics and giants have been assayed of whom 8 were considered clinically to be active, and the values obtained are shown in Fig 2. Apart from two high values (one in a non-active case), the range of assays is the same as in the normal group. No statistically significant difference exists between this group and the normals, nor between the active and inactive cases.

In cases of hypopituitarism from various causes the assay values were significantly lower than in normals, and the values lie mostly at or below 90 µg/l. (Fig 3). Two cases are shown in Fig 3 who had pituitary stalk section for recurrent Cushing's disease and in these, the assay fell from the normal range to 20 and 40 µg/l. in five and ten days respectively.

Of 8 untreated cases of myxœdema studied, 4 have had assays of over 950 µg/l. and 4 have been

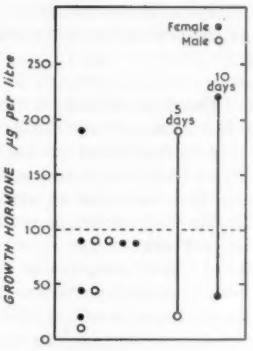

Fig 3 *Serum growth hormone levels in hypopituitarism*

normal (*see* Fig 4). Follow-up studies on treatment with thyroid in 2 cases have shown a fall in the assays, which reached the normal range after two months. Further studies on this group of patients are in progress.

Read (1960) and Hartog & Fraser (1961) have found significantly raised GH levels in active acromegaly, compared with their range for normal of 88 to 256 µg/l. Seven of our assays on acromegalics would be considered raised by these workers. However, 5 of these assays lie within our normal range, even though 3 of them are active cases.

Various possible explanations for our failure to demonstrate a significantly raised assay in active acromegaly can be considered. The presence of

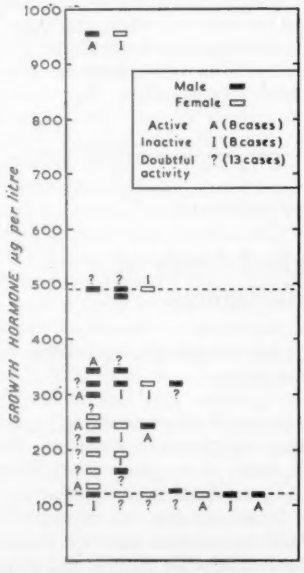

Fig 2 *Serum growth hormone levels in acromegaly*

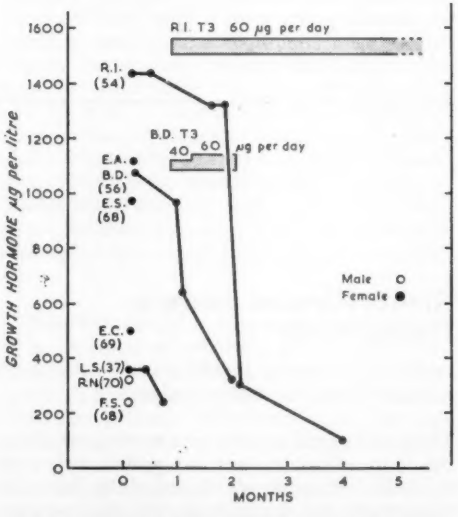

Fig 4 *Serum growth hormone levels in myxœdema*

more than one antigen in the material used in the production of antiserum might invalidate the assay. Previous work (Boucher 1960) has shown that the GH used in these studies does contain two antigens which show no immunological evidence of similarity. Further studies (in the press) show that the second antigen-antibody system has no effect on the assays obtained in any of the

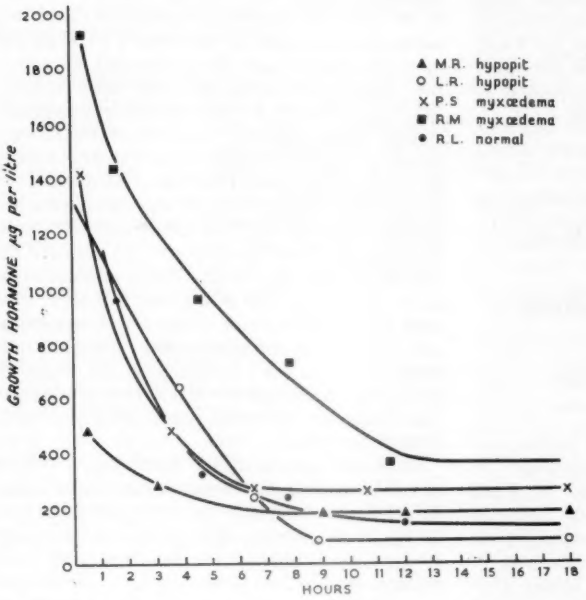

Fig 5 *Effects of intravenous growth hormone on serum levels*

groups described above. This means that if the second component possesses GH activity or represents some breakdown product of GH it is certainly not being assayed. Further work on this material is in progress.

Should GH in acromegaly differ from that in normals, it might be more sensitive to handling or altered in some way *in vivo* so as to lose, or partly lose, its immunological activity and thus fail to be fully detected in the assay. If this were so one could also postulate the formation of an antibody to GH which would reduce the titre in acromegalic sera. However no prozone of agglutination has been noted with the higher concentrations of these sera during the assays, so that this explanation is thought to be unlikely.

Another approach to the problems has been to consider whether the rate of utilization differs from normal in any group of patients. GH has been given intravenously in doses of 2–3 mg and its rate of disappearance from the blood has been measured. Although no conclusions can be drawn from this type of experiment as to the handling of endogenous GH it was thought that any gross differences found might point to some alteration in handling or metabolism of GH. The results obtained are shown in Fig 5. The values of serum GH within half an hour of injection rose in a normal subject, and in 2 hypopituitary and 2 myxœdemic subjects by from 300 to 1,500 μg/l., and the levels fell within six to twelve hours to the known basal values. The levels obtained declined with half life of 2·25 hours in the normal and 2·13 and 2·6 hours in the hypopituitary subjects. Neither of the myxœdemic patients had a high basal assay so that the finding of half lives of 1·85 and 3·5 hours, neither of which is significantly different from the others, is of interest, but further cases must be studied before any comment on the raised levels in some cases of myxœdema can be made.

Two acromegalic patients were given 3 mg of GH intravenously. In one, an active case, no rise could be found in the 5-minute sample. In the other,

probably inactive, the assay level rose from 120 to 160 μg in three minutes after the injection, but fluctuated between these levels over the day. This doubtful rise cannot be compared to that seen in the other subjects. There being no obvious technical reason for these findings it is possible that there is some alteration in handling of GH or at least of exogenous GH in acromegaly.

From these results it appears that we are unable to assess activity in cases of acromegaly or gigantism by the assay of GH levels in the serum. More cases of acromegaly of well-defined activity must be studied before one can say whether the handling of a load of GH may distinguish the active cases. At present the assay is most reliable in distinguishing cases of hypopituitarism.

REFERENCES
Boucher B J (1960) *Nature, Lond.* **188**, 1025
Hartog M & Fraser R (1961) *J. Endocrin.* **22**, 101
Read C H (1960) *In:* Clinical Endocrinology I. Ed. E B Astwood. New York; p. 598
Read C H & Stone D B (1958) *Amer. J. Dis. Child.* **96**, 538

Immunoassay of Growth Hormone in Human Serum

by R M Ehrlich MD & P J Randle PhD MB
(*Cambridge*)

An immunological assay for growth hormone in human serum employing hæmagglutination inhibition has recently been described by Read (1960). The method of assay depends upon the fact that erythrocytes coated with human growth hormone (HGH) prepared by the method of Raben (1959) are agglutinated by rabbit anti-HGH serum and that prior addition of a definite quantity of HGH to the antiserum will inhibit such agglutination. When a constant amount of antiserum and serial dilutions of HGH or human serum is employed, the HGH content of the serum may readily be calculated.

Experimental procedure: Sheep erythrocytes were treated with tannic acid as described by Read (1960) and then suspended in a solution containing 10 μg/ml of HGH prepared by the method of Raben (1959) from human pituitary glands obtained at autopsy. For assay of HGH, 0·1 ml of a 1% suspension of HGH-coated erythrocytes, 0·1 ml of serial dilutions of human serum (1 : 2 to 1 : 80) or of HGH (0·075 to 0·005 μg/ml) and 0·1 ml of an appropriate dilution of antiserum were mixed in small round-bottomed tubes of as uniform a shape as possible and run in duplicate. The diluent in each case was normal rabbit serum (1 : 150 in 0·15M phosphate buffer pH 7·2). The tubes were allowed to stand at room temperature for four to twelve hours and the presence or absence of agglutination defined by the pattern of settling (Stavitsky 1954). Since the titre of antiserum was found to vary by a small but significant amount each day it was particularly important to measure the titre of the antiserum immediately before each assay. The final dilution of antiserum employed was approximately the titre.

Results: The concentration of HGH in random samples of serum from normal adults was found to be 19·5±0·7 μg/100 ml (mean±S.E.M.): the range of concentrations was from 9 to 30 μg/100 ml in 24 subjects (ages 20 to 40 years). Several of the samples were reassayed many times and the values obtained on different days were essentially similar. When different amounts of HGH were added to normal human serum approximately 80–100% of the added HGH was recovered in the assay. After fasting overnight the values were not significantly different from those recorded above, though experiments to date have not excluded the possibility that the serum HGH concentration may be lower in the post-absorptive state than after fasting. The mean serum HGH concentration in ten hypophysectomized patients was reduced to 12·2±3·3 (range<2 to 29). In serum from seven acromegalics the HGH concentration was frequently increased (mean 30·8±2; range 22 to 56 μg/100 ml).

In normal pregnancy the serum concentration of HGH was found to be within the normal range. In successive trimesters the concentrations were 22·5±2·8 (8 subjects) 20·7±1·2 (15 subjects) and 19·2±1·7 (13 subjects). On the other hand, in 10 patients studied two to ten days *post partum* the mean HGH concentration was found to be increased (mean 36±4·4; range 21–66).

Comment: These results confirm the conclusion of Read (1960) that an immunological assay for HGH based on hæmagglutination inhibition can be successfully applied to the estimation of HGH in serum. The values which have been obtained for serum of normal adults are very similar to those of Read but lower than those reported by McGarry *et al.* (1960). Our findings also confirm that the serum concentration of HGH may be increased in some cases of acromegaly and reduced in hypophysectomized patients. The finding of values within the normal range for serum HGH concentration in 6 of 10 patients hypophysectomized by surgery or irradiation could be explained if these patients had sufficient residual pituitary tissue to maintain near normal serum HGH concentrations. Recent work of Campbell (1959) has emphasized the functional significance of minute amounts of pituitary tissue remaining after hypophysectomy.

Serum HGH concentrations in pregnancy and in the post-partum period have not previously been recorded. Our findings indicate that the concentration is normal during pregnancy but increased in the post-partum period. This is of special interest because of the known requirement for growth hormone in mammary gland development and in milk secretion (Lyons *et al.* 1955) but more particularly because it is known that the administration of growth hormone to animals in declining lactation leads to a resurgence of milk production (Cotes *et al.* 1949).

Acknowledgments: The HGH used in these investigations was prepared by Dr H B F Dixon in the Department of Biochemistry, University of Cambridge, and obtained from the Clinical Endocrinology Committee of the Medical Research Council. The cost of these investigations was defrayed in part by grants from the Medical Research Council and the British Diabetic Association. It is a pleasure to thank Professor F G Young for his interest in these studies.

REFERENCES

Campbell H J (1959) *J. Physiol.* **149**, 394
Cotes P M, Crichton J A, Folley S J & Young F G (1949) *Nature, Lond.* **164**, 992
Lyons W R, Johnson R E, Cole R D & Li C H (1955) *In:* The Hypophyseal Growth Hormone. Nature and Actions. Eds. R W Smith jr, O H Gaebler & C N H Long. New York; p 461
McGarry E E, Fishman J, Lesnoff A, Simpson R, Lucius J, Ballantyne A & Beck J C (1960) *Acta endocr., Copenhagen.* Suppl. 51, 299
Raben M S (1959) *Recent Prog. Hormone Res.* **15**, 71
Read C H (1960) *In:* Clinical Endocrinology I. Ed. E B Astwood. New York; p. 598
Stavitsky A B (1954) *J. Immunol.* **72**, 360

The Immunological Assay of Growth Hormone [*Abstract*]

by M Hartog BM MRCP and
Russell Fraser MD FRCP (*London*)

The paper described the technique, its accuracy and the results obtained in 18 normal subjects, 11 patients with acromegaly and 7 hypophysectomized patients. This work has recently been published (*J. Endocrin.* **22**, 101).

In addition results in 5 patients with active acromegaly who had been treated by pituitary implantation were presented. Two of these patients experienced no improvement following implantation of ^{198}Au and their serum GH values were unchanged. Another patient whose serum GH was also unchanged experienced some improvement following ^{198}Au. Two patients had clear clinical improvement, one following ^{198}Au and the other following ^{90}Y implantation, and their serum GH values fell significantly from their pre-implant figures.

Immunological Study of Human Gonadotrophins

by W R Butt PhD ARIC, A C Crooke MD MRCP and F J Cunningham BSC (*Birmingham*)

There is an extensive literature on the early work on antibodies or antihormones to gonadotrophins which has been fully reviewed by Zondek & Sulman (1942) and by Evans & Simpson (1950). Interest in the subject has been renewed by the preparation of purer hormones and by more recent developments in immunological techniques (Henry & van Dyke 1958). Recently Wide & Gemzell (1960) and Brody & Carlström (1960, 1961) have claimed to have developed immunological assays for chorionic gonadotrophin as a test for pregnancy. We have been interested in cross-reactions between different gonadotrophic antigens and antisera which suggest that they may be unspecific (Butt *et al.* 1960).

Antisera have been raised against gonadotrophins from the urine of both postmenopausal (HMG, human menopausal gonadotrophin) and pregnant women (HCG, human chorionic gonadotrophin) and also from human pituitary glands (HPG). The extracts from the urine of postmenopausal women have been purified using ion exchange materials by methods described previously (Butt *et al.* 1959) and HCG was supplied by Leo Pharmaceutical Products Ltd (Copenhagen). Human pituitary preparations supplied by Dr A Korner of the Department of Biochemistry, Cambridge University, were fractionated on columns of carboxymethyl (CM) cellulose and diethyl aminoethyl (DEAE) cellulose and calcium phosphate (CP) (Butt, Crooke & Cunningham, in press).

The antigens were dissolved in saline and mixed with an equal weight of bentonite to which they adsorb strongly. 2·0 ml of the suspension, usually containing 0·5 mg protein were given intravenously to rabbits twice a week for three or more weeks. Biologically active antisera have been obtained against HMG, HPG and HCG using the following amounts of protein:

(1) HMG 20 mg of the DEAE fraction having a total potency equivalent to 300 mg of the International Reference substance, HMG24.
(2) HPG 5 mg of the DEAE fraction having a total potency equivalent to 1,300 mg HMG24
(3) HCG 2·75 mg having a total potency equivalent to 4,400 i.u.

The activity of the antisera was tested *in vivo* using mice or rats. Each serum was injected intraperitoneally and the next day the antigen was given subcutaneously. Antisera to both HMG and

to HPG inhibited both HMG and HPG in mice but failed to inhibit the activity of HCG in rats. Antiserum to HCG, however, inhibited all types of gonadotrophin, HCG, HMG and HPG in mice and rats. This confirms our earlier observations (Butt *et al.* 1960).

In more recent experiments using the agar gel diffusion technique we have observed at least two precipitin lines when antiserum to HMG reacted with either HMG or with HCG but HPG purified to the stage involving chromatography on DEAE cellulose gave only one precipitin line. Further purification of this material on the CP column produced a fraction which had a potency equivalent to 3,000 mg HMG24 and this gave no precipitin lines against antiserum to HMG. The antigen which was responsible for the reaction in the cruder fraction was adsorbed more firmly on to the CP column but was biologically inactive. Antisera to HPG and HCG gave no precipitin lines with any of the gonadotrophic antigens.

A method has now been developed whereby precipitation can be observed in agar gel between antiserum to HCG and gonadotrophic antigens. Nigrosine W.S. (George T Gurr) was first incorporated into the agar gel and after allowing time for the diffusion of antigen and antibody to occur the excess dye was washed out. A dyed precipitin line was now observed where previously no reaction was visible. At least two lines could be seen when antiserum to HCG reacted with HCG or with HMG but when the antiserum was first mixed with HMG to absorb antibody and the absorbed antiserum was allowed to react with HCG only one line was visible in the nigrosine-stained agar gel.

Recently we have applied the red cell hæmagglutination technique, as modified by Ling (1960), to these substances. The absorbed antiserum to HCG agglutinated cells which had been sensitized with HCG and this reaction was inhibited by the addition of microgram quantities of HCG. It was not specific for HCG, however, since the fraction from HPG which was predominantly luteinizing hormone (LH) was also found to be a powerful inhibitor of agglutination. The fraction which was predominantly follicle stimulating hormone (FSH) was much less effective and fractions which were free of gonadotrophic activity, including growth hormone, were without effect.

Conclusion: The evidence so far suggests that antiserum to human chorionic gonadotrophin reacts with not only its own predominantly luteinizing hormone antigen but also the LH from human pituitary glands. The immunological assay of HCG as a test of pregnancy should therefore be accepted with reserve because of this lack of specificity. The antiserum to HCG is relatively much less effective against the mainly FSH fraction from HPG. Antiserum to the DEAE fraction of HPG, which is relatively rich in FSH, is effective against HPG and against HMG but is ineffective against HCG. This suggests that an antiserum which is specific for follicle stimulating hormone can be developed, and this problem is now under investigation.

Acknowledgments: The work was supported by grants from the Medical Research Council and the Endowment Fund Medical Research Committee of the United Birmingham Hospitals.

REFERENCES

Butt W R, Crooke A C & Cunningham F J (1959) *Acta endocr., Copenhagen* **32,** 509
Butt W R, Crooke A C, Cunningham F J & Gell P G H (1960) *J. Endocrin.* **20,** ix
Brody S & Carlström G (1960) *Lancet* ii, 99 (1961) *Nature, Lond.* **189,** 841
Evans H M & Simpson M E (1950) *In:* The Hormones II. Eds. G Pincus & K V Thimann. New York; p. 351
Henry S S & van Dyke H B (1958) *J. Endocrin.* **16,** 310
Ling N R (1960) *Biochem. J.* **77,** 12P
Wide L & Gemzell C A (1960) *Acta endocr., Copenhagen* **35,** 261
Zondek B & Sulman F (1942) The Antigonadotrophic Factor. Baltimore

Section of Urology

President M F Nicholls CBE MCh

Meeting February 23 1961

The Use of the Image Intensifier in Urology

Dr J J Stevenson (*London*)

For more than ten years image intensification has been playing an increasing part in the field of X-ray diagnosis. It has allowed deeply seated structures in the body to be seen clearly without previous dark adaptation of the eyes and in conditions of subdued room lighting. Moreover this can be effected with less dose to the patient, the radiologist and other observers.

Urological surgeons are well aware of the application of this new advance to their own specialty and although they may not yet have the equipment in their own centres they have had the opportunity of seeing it in use elsewhere. However, some have been hesitant to advise hospital authorities to spend a large amount of money on equipment which might have only limited applications, and upon the performance of which they had, themselves, certain misgivings. Those who wished to make a special study of inflammatory conditions in the kidney, obstructions at the pelviureteric junction, movements of the ureter, vesicoureteric reflux and the mechanisms at the bladder neck would have had to support the additional cost of cine-radiography. This addition might throw a considerable strain upon an already overworked X-ray department and would demand particular skill and virtuosity on the part of the radiologist concerned. Nevertheless, many of the larger centres have such equipment to-day and others are following.

We have been fortunate at the Institute of Urology to have had major facilities for image intensification and cine-radiography for several years and I have similar installations in two of my other departments. It is sometimes difficult when one has embarked on such projects to admit, especially to others, certain deficiencies which become increasingly apparent as time goes on. I refer particularly to the reflecting viewer part of the optical system of the type of intensifier most commonly used in this country. This is rather cumbersome and the exit pupil of light is so narrow that only one eye can be used for viewing. Too much light in the room causes loss of detail and it requires a special attachment for more than one observer to see at the same time. Although the image is bright and the intensity can be altered it is not possible to vary the contrast, thus fine detail may be missed completely. The 5 in. diameter of the screens of our early tubes only covered about 3 in. of a kidney or bladder on account of the magnification involved and this was barely sufficient.

The advantages of a television link have long been realized, and in 1952 at the Royal Marsden Hospital we made our first experiments. The results were poor, but we found that the system worked, and later at the Royal College of Surgeons in 1955 we again demonstrated the possibilities of the method. Limitations inherent in the intensifier tubes then available did not appear to make development worth while, but in 1959 when larger and more suitable tubes were about to appear we purchased the first of our camera chains in order to learn the new technique so that when we added television to our new 7 in. and 9 in. intensifiers last year relatively little trouble ensued.

The television equipment consists of a small camera which is attached to the image intensifier and two control units which together with an 8 in. monitor are accommodated in a movable console cabinet (Fig 1). The controls are relatively simple and our difficulties have been no greater than we expected. We have fitted a 14 in. monitor to a wall bracket which is more convenient for viewing with the patient supine and the hospital has been wired so that the picture can be transmitted to the operating theatre, lecture room or radiologist's office.

In urology as well as in the gastro-intestinal tract the facility of viewing the image in comfort on the monitor has been greatly appreciated while the ability to alter contrast at will allows much more detail to be seen. Indeed the improvement has been so great that we are now using the tele-

Fig 1 *Television camera with image intensifier*

vised image alone where cine-radiography was necessary before. Thus micturating cystograms are frequently performed with television and the fleeting ureteric refluxes can be observed.

Our patients are generally sent to the X-ray department for ascending pyelography with the ureteric catheter *in situ* and by means of the monitor in the operating theatre the surgeon can clearly see details of the kidney at the same time as the radiologist. The dose to the patient is relatively low and rarely exceeds 1 or 2 r/minute. Every effort is made to shield the gonads as much as possible. Other applications of television have been selective biopsy of metastatic lesions in bone, removal of ureteric calculi with a stone extractor, selective renal biopsy, aspiration of renal cysts and controlling the insertion of a cannula into the hypophysis for the purpose of introducing radioactive material. By means of a portable intensifier with television small renal calculi and debris have been removed in the operating theatre.

While the amount of cine-radiography has decreased, we have sought a method whereby this could be carried out without exchanging cameras and without in any way affecting the fluoroscopic picture. In order to film the monitor screen a special two-speed synchronous motor has been attached to our 35 mm cine camera and a phase-shifting transformer constructed so that the bands on the monitor shall not become visible on the film as the raster changes. We have not yet used this very much and the picture quality is inferior to that of the direct method. However, the results are promising and there is a considerable saving in dose.

The attractive possibility of electronically storing the televised image has long been envisaged (Mayneord 1955) by being able to continue to display it on a monitor for some minutes after the X-rays have been switched off. Thus, details of a kidney may be studied at leisure and in consultation, without further irradiation of the patient and without waiting for a film to be developed. This apparatus has been constructed in the Physics Department of the Royal Marsden Hospital using the English Electric E702 storage tube and has been more fully described elsewhere (Stevenson 1961).

Being a new development, detail is again not so good as on the conventional monitor but it is quite sufficient for the insertion of radioactive implants. There is little doubt that other techniques giving improved quality will become available during the next few years.

REFERENCES
Mayneord W V (1955) *Brit. J. Radiol.* **27, 309**
Stevenson J J (1961) *Brit. J. Radiol.* **34, 273**

Dr Frank Greenwood (*Uxbridge*)

Television Cine-radiography

Most radiologists have long welcomed consultation about X-ray films with their clinical colleagues and have benefited greatly from it. Consultation during screen examination has, however, been much more rare owing to the difficulty of simultaneous viewing and the excess radiation to the patient which any lengthy fluoroscopy has entailed. This difficulty was partially solved by the advent of the image intensifier with its reduced dosage but, even with mirror optics, viewing was still limited to two observers and was far from ideal. Television has provided an obvious and long-sought solution to the problem and moreover, by the use of remote monitors, is ideal for teaching purposes.

The development of television for fluoroscopy has proceeded on two distinct lines. In one, the image intensifier is retained and a Vidicon camera scans the output phosphor: in the other, the intensifier is omitted and an Orthicon camera

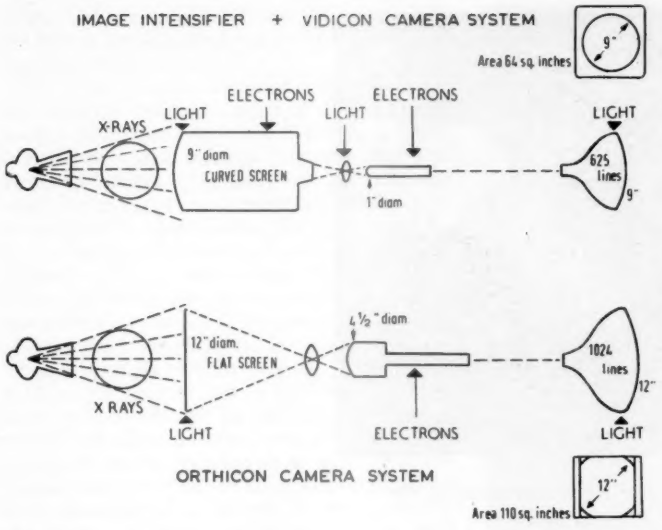

Fig 1

scans a modified conventional fluoroscopic screen. Fig 1 shows the basic differences between the two systems. It will be appreciated that the Vidicon camera is essentially an industrial development whereas the Orthicon is a very high grade precision instrument used in the difficult conditions of outside broadcasting. For this particular work the Orthicon camera has been modified from the standard television type by incorporating a wider target to mesh spacing in order to get a greater sensitivity. The Orthicon camera is more complex and therefore more expensive than the Vidicon and one obviously needs to find good reasons for using this and discarding the great light gain (over a thousand times) given by the image intensifier.

The three main advantages of the Orthicon camera system are:
(1) The increase in the size of the field from a circular one of 64 sq. in. (the largest practicable with the intensifier) to a rectangular field of 110 sq. in. This increase is obviously of less importance in urology than in thoracic or cardiac work.
(2) The increased definition of the monitor which is obtained by (*a*) the much more elaborate construction of the Orthicon tube and the increase in size of its photocathode to $4\frac{1}{2}$ in. as against 1 in. diameter of the Vidicon and (*b*) the elimination of a complete light-electron-light sequence in the intensifier. Though this sequence increases the brilliance, definition is lost in the same way as it is lost when printing from a negative in photography.
(3) The improved grey scale and the adoption of a 1,024-line system in place of the 625-line type.

Obviously certain disadvantages must be put in the other scale. These are:
(1) Expense.
(2) The greater bulk of the equipment, though this is to a large extent capable of being offset by good engineering.
(3) Restriction of cinematograph work to filming from the television monitor. This necessitates phasing the camera speeds to the cycles of the input main to avoid stroboscopic effects. Fortunately two possible speeds – 25 and $16\frac{2}{3}$ frames per second – are almost identical with sound and silent projection speeds.

The apparatus has great versatility: the monitor can show either negative or positive images, the image can be magnified by 2 by the Orthicon camera and can be inverted. Inversion of the image is not of great importance in pyelography unless an extreme Trendelenburg position is required but for femoral arteriography or cardiac catheterization it does allow approach to either limb from the free side of the table and viewing or filming without inversion of the image. Finally, by using a lens of 25 instead of 15 mm focal length the film image can be further magnified by 2.

On general principles it is essential that costly apparatus of this type which will certainly not be in use throughout the day should be readily detachable from a standard X-ray table, which can then be used for routine work in the department, and because very many patients having

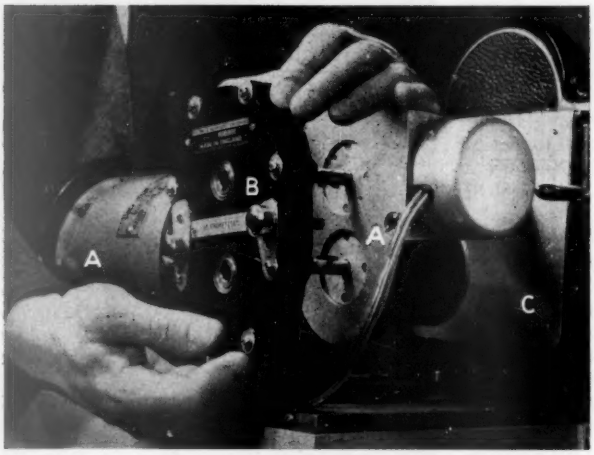

Fig 2 A, *The polarized phased motor.* B, *The gear change.* C, *The cine-camera*

gastro-intestinal examinations will require ordinary films rather than cine-radiography the screen carriage should have facilities for the exposure of ordinary radiographs and a serial device and compression cones. This applies to a large extent also to urological work. This is best achieved by ceiling mounting of the whole lens and Orthicon system so that it can be readily replaced by a conventional fluoroscopic screen. By doing this it is also possible to use the table for standard radiography with an overhead tube.

In cases of hydronephrosis, cine-radiography demonstrates the surprising degree of activity persisting in both the dilated calyces and the ureter – a point which had not been appreciated when standard radiography was employed. The converse of this is shown in tuberculous lesions where dye will remain in an affected calyx despite very active peristaltic activity of the other calyces. Experimental work designed to illustrate the variations of radiographic technique possible with this apparatus, such as reversal, inversion and magnification of the image, has been carried out using the post-mortem kidney filled with barium. One classic example of pyelovenous backflow was noted. The pressure of the fluid injected into the ureter in this case was very low but attempts to repeat this were quite unsuccessful even though very high pressures were used. This may be of interest in view of the diverse views held of the nature of pyelovenous backflow. [Films were shown to illustrate these points.]

Negative film can be processed in the X-ray department and viewed within about two hours. Using this film and a positive monitor image probably gives the greatest radiographic detail but, when the X-ray beam is coned or shuttered down, the surrounding unexposed area of the film is very distracting. Printing in positive eliminates this but the cost is high and it may be found equally satisfactory to film the negative screen image or to use reversal film.

The polarized phased motor, camera and gears (Fig 2), together with the television monitor, can be installed outside the X-ray room thus saving space and eliminating noise. Additional monitors can be placed in other parts of the hospital at distances up to 1,000 ft from the X-ray room.

As regards future developments; 70 mm or 100 mm still films can certainly be taken by substituting the appropriate camera for a cine-camera. There are two other fascinating possibilities: (1) Recording by videotape. (2) The use of a storage tube for later viewing of a television image. We are, I am sure, only in the early stages of a most interesting new era in radiology.

Mr Howard G Hanley (*London*)

Dr Stevenson and Dr Greenwood have presented the technical and radiological aspects of the two major systems of X-ray intensification available to-day. The purpose of this paper is to present a balanced or even restrained assessment of the value of this new radiological advance to the practising urologist, and where possible to indicate the pros and cons of various techniques from the clinician's point of view.

I must commence by expressing my gratitude and appreciation to both Dr Stevenson and Dr Greenwood, for it is obvious that I am fortunate

indeed to have had the privilege of working with the two accepted authorities on this new radiological development.

This raises perhaps the most important necessity from the urologist's point of view, which is, cordial relationship with the X-ray department. It would be a great mistake to imagine that once an image amplifier has been installed in a hospital, the urologist can immediately benefit from the undeniable advantages of this apparatus without a considerable amount of personal effort and attention. Unless the urologist is prepared to devote the time to the apparatus himself, he might just as well do without it, because the chief value of the whole principle is for him to see for himself what is happening in the calyces, pelvis, ureter, bladder and urethra, not to rely on what some other person tells him he has seen. This means that the apparatus must be conveniently accessible. Ideally, it should be possible to perform cystoscopies and other minor surgical procedures in the X-ray department, for only by this means will the great advantages of fluoroscopy be fully realized. Failing this, and a poor second, the apparatus must be situated close to the operating theatre, but both possibilities emphasize the importance of the closest co-operation between radiologist and clinician.

Patient dosage: For the urologist, the long-desired ability to see and study the dynamics of the urinary tract has at last been achieved with relative safety. It is important, however, to note the phrase 'relative safety'. It must be realized that although the X-ray dosage received by the patient is considerably reduced by screening with an amplifier as compared with conventional fluoroscopy, it is still not negligible. The important point is that a much greater amount of accurate information may be obtained for a given X-ray dosage when using amplification. The great danger is that one becomes engrossed in what one is seeing and unless strict precautions are taken the patient may receive more, not less irradiation.

However, in selected cases, and it must be remembered that the system should only be used in selected cases, the ability to watch the movements of the urinary tract or to perform special procedures under visual control, has opened up a new chapter of diagnosis and therapy in urology, quite apart from the already recorded achievements in teaching and research (Hanley 1958, 1959, 1960).

Types of apparatus: The various types of apparatus are not all equally convenient from the urologist's point of view; some are most unsuitable. The basic essentials are that it should be possible to view with both eyes in comfort, without having to climb into awkward positions, and that at least two people must be able to view simultaneously. It must be possible to take immediate spot films without movement of patient or apparatus, and if one is going to make use of the cine camera, it must be possible to change from viewing to spot film to cine work with ease and rapidity. All of these requirements are met by the most modern forms of apparatus, while the television monitor has extended the possibilities beyond our first thoughts (Fig 1).

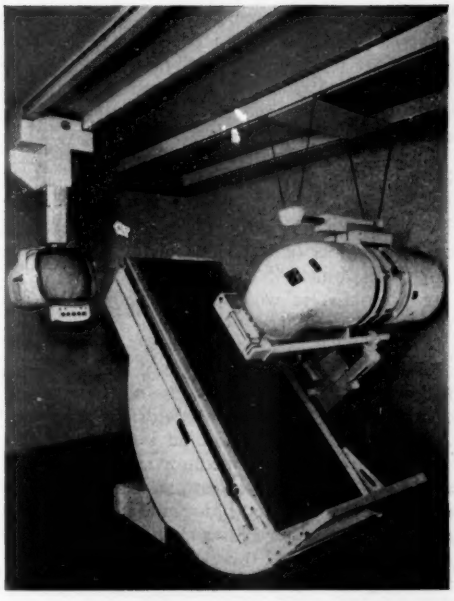

Fig 1 *The Orthicon camera unit is suspended over the table in such a way that continuous fluoroscopy is possible whilst the patient is being tilted into the vertical position. This is a most valuable facility when studying the emptying of the renal pelves and ureters. When the table is required for conventional radiography, the whole amplifier unit can be detached and moved out of the way on the overhead rail. The special 1,024-line monitor tube, which is adjustable for height and direction, is seen on the left*

Size of field: The old so-called 5 in. tube was frequently too small to visualize the whole of one large kidney, but tubes with a field of 7 or 9 in. are now available while the Marconi Orthicon system has a 12 in. field which adequately covers both kidneys simultaneously (Hanley *et al.* 1961).

However, agreeable as a very large field may be, those who do not possess a modern tube should not be too depressed. The urologist can only watch one kidney at a time even if two appear on the screen simultaneously, and the present 7 in. tube at St Paul's Hospital has a satisfactory field

for most urological purposes. In practice more valuable information can be obtained by 'panning' over the tract using a small field than by trying to see too much at the same time on a large field, while in general the smaller the field the sharper the picture.

Clinical Applications

Much has been written about the various uses of the intensifier in urology, but it must be repeated that regardless of the technical abilities of the apparatus, unless it is simple and accessible to the urologist, it will not be used to its full advantage.

Excretion pyelography: In spite of improvements following the introduction of the newer tri-iodine compounds, the value of intensification in excretion pyelography is limited by the relatively poor contrast of the medium excreted by the kidney. This means that the standard I.V.P. examination is still required in the preliminary assessment of every case. However, having made this preliminary survey there are occasions when screening under the amplifier may give most valuable added information, particularly in children and thin persons. Using double-dosage injections of Hypaque it has been possible to study the emptying from the pelvi-ureteric junction in doubtful cases of hydronephrosis thereby distinguishing between a tonic junction and a true obstruction, without the complicating factor of a foreign body in the form of a ureteric catheter. On occasion a micturating cystogram in a child may be possible without the necessity of catheterization. In general, however, one seldom uses the amplifier in routine excretion pyelography, although its value in the localization of special areas of the kidney, either for renal biopsy or the aspiration of large cysts, &c., is obvious (Fergusson & Stevenson 1960).

Retrograde pyelography: Ascending pyelography has been completely revolutionized by the ability to watch the pelvis whilst it is being filled. Not only can the dynamics be studied during this filling phase, but a spot film can be exposed at the correct moment thus avoiding the frustration and danger of under- or over-filling respectively. When the spot film has been developed the catheter is withdrawn and the emptying pattern of the pelvis can be studied so that the maximum amount of information is obtained in the minimum time. The quality of the spot film is excellent while the additional information to be obtained from the visual screening is such as to make one wonder how it was ever possible to do without these facilities which will surely become standard urological practice in the future.

Other Specialized Uses

Cystography: Considerably more valuable information has been obtained from a micturating cystogram since we have been able to watch the process as it occurs (Hanley *et al.* 1961). Transient ureteric reflux, which is not uncommon, may be missed by a series of spot films, but can be clearly seen on the screen. This is one type of investigation which is greatly helped by a cine film record.

Renal puncture: During the course of an excretion pyelogram the contrast obtained may be insufficient to show fine detail of the calycine pattern on a monitor screen, but it is more than enough for accurate localization, so that renal biopsy from any chosen area of the kidney becomes a simple procedure.

Similarly the aspiration of renal cysts can now be carried out with great accuracy, but a note of caution is necessary here. When the diagnosis of solitary or even large multiple cysts is certain, aspiration is a safe and effective treatment. The distortion of the calycine pattern is decreased and this has been maintained in all of our cases which we have been able to follow up (in one patient for as long as five years). However, even though aspiration is the most accurate form of diagnosis available to-day it is questionable whether it is justifiable for purely differential diagnostic purposes. If the diagnosis is wrong it cannot possibly be a good thing to insert a needle into a renal tumour, even if an immediate nephrectomy is contemplated. A personal experience of thirteen aspirations so far has been instructive. In each case the presumptive diagnosis of a cyst was confirmed by a very experienced radiologist. In two patients the diagnosis was in some slight doubt, and, in fact, solid tumours were found on aspiration. It is interesting to add that in one of these patients a subsequent aortogram showed all the appearances of a cyst, but surgery proved it to be a tumour. In another patient, the fluid aspirated was at first clear, but became blood stained during the course of the investigation, and this subsequently proved to be a carcinoma in the base of a cyst. A further patient, with an irregular-shaped cyst which was subsequently shown to have a small tumour inside it, had clear fluid on aspiration. The presence of clear fluid may therefore be no proof of the absence of a neoplasm and it would appear that in spite of being able to aspirate cysts under direct visual control, a space-filling renal lesion must still be explored if there is even the remotest doubt about the diagnosis.

Operating theatre use: One advantage of the small mobile intensifier tube is that it can be used, perhaps in conjunction with a second tube, for localization in two planes, and Mr J D Fergusson and

others use this principle regularly for the introduction of yttrium grains into the pituitary fossa in prostatic cancer cases.

A small portable tube can also be used in the operating theatre for the localization of renal calculi, but the value of the method is limited by the density and size of the stone. One requires such help, not for large stones, but for the localization of small concretions or fragments left behind, and it is in such cases that the intensifier is of least value. Improvement will undoubtedly occur as newer forms of apparatus are devised, but at the moment a small X-ray film in contact with the exposed kidney remains the best way of pin-pointing these small particles.

Cine-radiography

It should be clearly understood by urologists that at the present time there is a great division between the very obvious advantages of visual screening and the much more complex problems associated with a cine camera. We have now had considerable experience with cine-pyelography using 35 mm and 16 mm cameras, both of which originally had advantages and disadvantages. However, the high cost of 35 mm film, and the fact that it generally requires to be processed professionally and reduced to 16 mm before it can be projected in a hospital, are very great disadvantages. On the other hand 16 mm film can be processed and projected in the X-ray department within a few hours of exposure, while the modern system of photographing the television monitor provides abundant light and contrast so that fine-grain film can be used, and there would now appear to be no advantage in using 35 mm film.

There is no doubt that cine-radiography is a most valuable adjunct to X-ray intensification, and in certain specialized instances a cine-film record of the dynamics of a pelvis, ureter or bladder may be invaluable, while for research and teaching purposes the cine camera has opened up a whole new vista of urological thought.

Nevertheless, the cine work is time-consuming and frustrating owing to the number of things which can go wrong and one would be well advised to use the camera regularly or not at all, because its casual use will rarely produce a film of the one special case just when required.

In order to achieve the full benefit from a cine camera it must therefore be used regularly in a busy department, because only then will it be ready and available at short notice. As already stated for research and teaching purposes the camera is invaluable, but it must be repeated that for routine clinical work it is seldom called for. The essential factor is the ability to see clearly with both eyes some form of screen or monitor, and to be able to take good quality spot films at a moment's notice.

In conclusion one would say that, although simple visual screening during pyelography will certainly become routine urological practice, cine-pyelography may remain the perquisite of the larger research or teaching units.

REFERENCES

Fergusson J D & Stevenson J J (1960) *Brit. J. Urol*, **32**, 484

Hanley H G
(1958) *Congr. Soc. int. Urol.* **2**, 29
(1950) *Brit. J. Urol.* **31**, 484
(1960) *Lancet* ii, 664

Hanley H G, Greenwood F G & Scott M E
(1961) *Brit. med. J.* i, 1310

Parts of Dr Greenwood's and Mr Hanley's papers have already appeared in the *British Medical Journal* (1961, i, 1310) and are reproduced by kind permission of the Editor.

Meeting March 23 1961

The following cases and specimens were shown:

Hamartoma of the Kidney
Mr J P Hopewell

Carcinoma of Urethra after Cystectomy for Tumour in Diverticulum: Urethrectomy
Mr A H Jacobs

Tuberculous Epididymitis in a Child of 5 Years
Mr R A Mogg

Bladder Diverticulum causing Hydronephrosis
Mr A E Roche

Carcinoma of the Prostate with Secondaries in the Testis
Mr R S Murley

Two Specimens of Bilateral Testicular Tumours
Mr T M Robinson (for Mr M F Nicholls)

Malignant Lymphoma of Testicle
Mr J F R Ingall (for Mr R Cox)

Books recently presented and placed in the Society's library

Abrahams Sir Adolphe
The disabilities and injuries of sport
pp 95 12s 6d
London: Elek 1961

Asociación Argentina de Anestesiologia
Quinto congreso Argentino de Anestesiología 23 al 19 de Octubre de 1955
Buenos Aires: 1956

Association for Research in Nervous and Mental Diseases
Neuromuscular disorders (the motor unit and its disorders)
Proceedings vol. 38 pp 813
Baltimore: Williams & Wilkins 1960

Baruffaldi O & Divano N
La spina bifida. Relazione svolta al XXIX congresso della Societa Piemontese Ligure Lombarda di Ortopedia e Chirurgia infantile, Genova, 25 Gannaio, 1958
pp 148
Padova: Cedam 1959

Brocher J E W
Die Wirbelsaulenleiden und ihre Differentialdiagnose. (Fortschritte auf dem Gebiete der Rontgenstrahlen, Ergänzungsband 68)
2nd ed pp 457 DM 128
Stuttgart: Thieme 1959

Browning E
Toxicity of industrial metals
pp 325 50s
London: Butterworth 1961

Buckstein J
Clinical roentgenology of the alimentary tract
pp 652
Philadelphia: Saunders 1940

Buytendijk F J J
Pain. Translated from the Dutch by E O'Shiel
pp 190 25s
London: Hutchinson 1961

Dawson W S
Aids to psychiatry
Edited by E W Anderson
8th ed pp 310 12s 6d
London: Baillière 1960

Farr A D
A laboratory handbook of blood transfusion techniques
pp 135 17s 6d
London: Heinemann 1961

Finerty J C & Cowdry E V
A textbook of histology: functional significance of cells and intercellular substances
5th ed pp 573 82s 6d
London: Kimpton 1960

Finochietto E & Finochietto R
Técnica quirúrgica: operaciones y aparatos
Vols. 2–3
Primera parte: técnica general
Buenos Aires: Ediar Soc. Anon. Editores 1944–1946

Folkard M S
A sociological contribution to the understanding of aggression and its treatment
pp 176 7s 6d
Coulsdon: Netherne Hospital 1960

Fourman L P R
Calcium metabolism and the bone
pp 325 37s 6d
Oxford: Blackwell 1960

François J
Les cataractes congénitales
pp 853
Paris: Masson 1959

Fulton J F
A bibliography of the Honourable Robert Boyle: Fellow of the Royal Society
2nd ed
pp 217 50s
Oxford: Clarendon Press 1961

Golden R
Diagnostic roentgenology
2 vols
New York: Nelson 1941

Gordon G C
Congenital deformities
pp 128 37s 6d
Edinburgh: Livingstone 1961

Hazell K
Social and medical problems of the elderly
pp 216 30s
London: Hutchinson 1960

Hieger I
Carcinogenesis
pp 138 35s
London & New York: Academic Press 1961

Hoffmann A
Funktionelle Diagnostik und Therapie der Erkrankungen des Herzens und der Gefässe
pp 483
Wiesbaden: Bergmann 1911

Karunaratne W A E
Scientific research
pp 172
Colombo: Colombo Apothecaries' Co 1952

Karunaratne W A E
Before evening falls: essays and addresses
pp 262
Colombo: Catholic Press 1957

(*Continued on p* 670)

Section of General Practice

President L W Batten MRCP

Meeting April 19 1961

Sore Feet

Dr R N R Grant (*Workington*)

A very powerful gambit or ploy in the art of being one up on one's patients is to ask an unprepared patient to show his feet. The changing expression of horror and shame followed by a lame apology show the neglect to which the feet are usually subjected. On the whole it is remarkable how little trouble they give.

So that we may consider how to remove the soreness from as many feet as possible, I must first consider what are the main causes of sore feet in general practice. For this purpose I have examined the figures from the Morbidity Survey carried out by the College of General Practitioners in collaboration with the General Register Office a few years ago, and my own figures for the same year, which do not differ greatly from these of the Morbidity Survey (Table 1).

Table 1
Morbidity Survey: patients per thousand at risk

Sprained ankle	8·5
Other injury	7
Chilblains	4
Tinea, Hyperhidrosis	6
Others	4

The last figure in Table 1 for other diseases is an understatement, as many sore feet remain undiagnosed and therefore unclassified. In my own practice of 2,500 I saw 115 patients with sore feet in one year, and in 2% of total consultations. Analysis in total numbers is shown in Table 2.

The only reason I saw one case of hallux valgus was because the corn on the bunion had gone septic.

But perhaps this is not quite the whole picture of sore feet. I have recently been favoured by a forward-looking County Medical Officer of Health for an experiment in having a Health Visitor attached to my practice. At the same time a free service for old or handicapped people was started by the County Health Service. I have been able to send our Health Visitor to examine as many old people's feet as possible whether they complained of sore feet or not, and to arrange for chiropody where necessary. The figures are not yet sufficient for detailed analysis but suggest that about half the patients aged over 70 require chiropody for their corns in order to be able to get about their houses and do necessary shopping in reasonable comfort. Many cases of hallux valgus have been observed but very few of these patients would admit to pain or inconvenience.

Table 2
Analysis of 115 patients with sore feet seen in one year

	M	F	
Sprained ankle	14	12	
Other injuries	14	10	(Includes those where secondary sepsis is the important factor)
Fractures	4	2	
Chilblains	—	11	
Hyperhidrosis	5	2	
Tinea	5	—	
Eczema and dermatitis	1	4	
Ingrowing toenail	3	2	
Painful heel, male type	3	—	
Painful heel, female type	—	2	
Tenosynovitis	1	1	
Plantar fasciitis	2	—	
Metatarsalgia	—	2	
Calcaneal spur	—	1	
Hallux valgus	—	1	
Osteoarthritis	2	1	
Other diseases and conditions of the feet	4	5	

I would like now to make a few comments on these commoner causes of sore feet with a view to prevention or avoidance of discomfort.

Accidents: Heavy industry is inevitably associated with accidents. Comparative sex figures for

sprained ankle give little support to the idea that high-heeled shoes may cause sprained ankles. I think that the more significant factor is the firmness with which the heel is held by the shoe.

Corns: Most of these are produced by pressure and friction of the toes on the relatively rigid part of the upper where it is joined to the sole.

Chilblains: In my own experience all the foot chilblains were on women's feet. We must accept the association of the condition with cold weather, against which fine stockings and fashion shoes are very inadequate protection. In fact, pressure from the shoes on the toes may so reduce the skin circulation as to promote chilling of the toes. There seems to be a general opinion that vasospasm in some way produces this condition but the negligible response to vasodilators suggests that this cannot be so. I think the condition must represent a breakdown of the normal local defence mechanism against cold when the arterioles relax and the arteriolar and capillary system is passively filled with blood from the normally functioning proximal arteries. If this reasoning is sound it would be more logical to treat this condition with drugs designed to restore the vascular tone, much as in the treatment of shock with noradrenaline. Such a mechanism might also explain the possibility of results being obtained by the popularly applied counter-irritants. For prevention, women's feet should be kept warmer and more freedom of movement of the toes should be allowed.

Tinea and hyperhidrosis: These are essentially diseases of men's feet – the two female cases being schoolgirls of 8 and 11. There appears to be a positive association with boots, particularly rubber boots, with lace-up shoes and with hot feet generally. One must bear in mind the triad of sweaty hands, feet and armpits associated with anxiety. There is no doubt that, whatever the cause, much trouble could be avoided by better ventilation and keeping men's feet cool, particularly indoors.

Eczema and dermatitis: Rubber, dyestuffs and the materials used in the preparation of leather are potential sensitizers, particularly when closely applied to the feet, as in women.

Ingrowing toenails: This is largely a matter of education in nail cutting, but the problem would arise less frequently if the pressure on the nail from the toe cap and crowding of the toes could be avoided.

Over half the remaining 20% of sore feet consist of those sometimes troublesome and difficult conditions which involve the bones and joints of the feet.

The painful heel in men seems to be almost like a bruise of the subcutaneous tissue of the plantar surface of the heel and to be associated with crepe rubber soled shoes – in that avoiding such footwear seemed to stop it. The painful lesion on the back of the heel in the two women was apparently a bursitis and was associated with low-cut flat shoes which depended on pressure on the back of the heel to keep them on. The tenosynovitis on the dorsum of the foot (2 cases) appeared to be promoted by pressure of a too tight and rigid upper on a highly arched foot. I wonder how many of these cases of so-called plantar fasciitis and those where pain is attributed to a calcaneal spur are due to putting a highly arched foot into a flat shoe and putting a flat foot into a highly arched shoe or on to an arch support. Whatever may be the cause of metatarsalgia, most of them only hurt when squeezed laterally.

Footwear

The difficult problem for footwear manufacturers, therefore, is to find an acceptable compromise between protection from the weather and inanimate matter on the one hand, and avoidance of the troubles of confined feet on the other. Provided one takes sufficient care and has enough money to pay for them, I can find little quarrel with the compromise achieved in our present male footwear. If, however, we eliminate accidental injury from present consideration by insisting on suitable protective footwear for hazardous occupations, something might be done for the rest of the community and while not at risk.

Criteria for footwear: Improved footwear must therefore avoid pressure on the toes, compression of the foot, either side-to-side, end-to-end or vertically, must be reasonably warm outdoors in winter and reasonably cool indoors in summer, be well ventilated and yet give adequate protection against the weather. It should be acceptable in appearance and easy to keep clean. There is nothing new in these criteria so let me consider what is worn by those who cannot afford to conform to fashion and where the only purpose is practicality and comfort. My experience and research reveals two basic types which could meet most of the criteria I have mentioned.

The first is the thong-toe or toe-post type of sandal, which is a sole with just enough straps to keep it on, one of which goes between the first and second toes. I have a pair which I bought and wore in the Persian Gulf ten years ago. They were quite comfortable once I was used to having a strap between the first and second toes. By their construction they can hardly press anywhere and

the toe-straps positively prevent development of the highly offensive but not very troublesome hallux valgus. In this form they do not give any protection against inclement weather, the only consideration in the Persian Gulf being protection from the hot sand. Similar types are worn in many hot countries and have been developed particularly in Japan. I see no reason why they should not be modified for more formal wear possibly with two or three grades of arch to suit all types of feet from pes planus to pes cavus, particularly as it is not difficult to make fine nylon stockings to go with them.

The second type of footwear which has survived in various forms is that made of wood such as Dutch clogs or open types such as those worn by poorer country people in Switzerland. I was interested to find during the War that Dutch clogs gave much more comfort and protection from the cold wet ground than Army boots. A new descendant of the clog is now sold as a foot exercise sandal, and is clearly the most sensible type of footwear obtainable in this country. I felt obliged to come to this meeting in such footwear, having first persuaded the manufacturers to produce a black pair which I hope are not unduly obtrusive. I wore them for a week with determination while I got used to the unusual action but I now find I wear them for choice on getting up in the morning and as soon as I get home in the evening. The only disadvantages I find with them are that they are produced with only one shape of arch, and one cannot easily run very fast in them, but then running fast is a hazardous occupation for which specially designed footwear should be worn.

Acknowledgment: I am indebted to the Scholl Manufacturing Company Limited, London for supplying me with a pair of their foot exercise sandals.

Mr W Alexander Law (*London*)

Painful foot conditions can arise at all ages and in all parts of the foot: fore-, mid- and hind-foot and ankle. Bone or soft tissue lesions may be the basis of symptoms, and treatment has to be directed along medical, physiotherapeutic, manipulative and orthopædic lines. These various techniques are usually very closely interdigitated and the success of surgery often depends upon the faithful adherence to conservative measures in addition. The common conditions producing 'sore feet' as a presenting symptom complex are:

Foot strain and pes planus
Metatarsalgia in its various forms
Hallux valgus and rigidus
Hammer toes and claw feet
Painful heels – bursitis and spurs
Arthritic conditions
Osteoporosis – particularly post-traumatic
Various skin lesions such as plantar warts, corns and ingrowing toe nails
Vascular disorders

Flat foot: This deformity may result from an hereditary tendency, postural defect, trauma and occupational strain, obesity and endocrine upset. In some congenital cases bone anomalies are present such as accessory scaphoid or calcaneo-cuboid and calcaneo-navicular fusion. Incipient flat foot or foot strain produces pain, fatigue and limp – the pain being characteristically worse on standing rather than walking. In very acute cases rest in bed may be necessary at first, followed by exercise therapy, supplemented on occasions by heat, massage, faradic and contrast foot baths and particularly by the wearing of correct footwear. The Thomas heel is invaluable and tends to make the patient walk on the outer border of the foot, and sometimes, if the hallux is not reaching the ground correctly, an $\frac{1}{8}$ or $\frac{1}{4}$ in. outer sole raise may also be necessary. Gym and ballet shoes should only be worn for the appropriate periods and barefoot walking avoided except on sand. In more resistant cases resilient rather than rigid metallic arch supports may be indicated, and in some severe cases in children plaster correction is required, with the feet inverted and forefeet pronated, the heel being maintained in the neutral position. The peroneal spastic flat foot was described by Sir Robert Jones in 1897, and Harris & Beath (1948) drew attention to the ætiological factor of the calcaneo-navicular and talo-calcaneal bar, partial or complete. These cases were frequently treated by prolonged plaster immobilization, peroneal tenotomy and peroneal nerve crushing, but a subastragaloid or triple arthrodesis may provide the most satisfactory method of relieving pain and deformity. Operations for pes planus, such as those of Miller (1927), Hoke (1931) and Grice (1952), are based on fusing the scapho-cuneiform and cuneo-metatarsal joints with a bone block, with the longitudinal arch moulded into a corrected position, or fusion of the tarsal tunnel.

Metatarsalgia: Yielding of the transverse arch results in pressure being taken on the heads of the second and third metatarsal bones, instead of the normal pressure being borne only on the first, fourth and fifth metatarsal heads. In childhood 'Freiberg's infraction' of the metatarsal head may occur as the result of trauma producing interference with the circulation in the epiphysis of the second or third metatarsal. March fracture is not an uncommon cause of forefoot pain and frequently the diagnosis is not made until the lesion is well advanced and callus palpable clinically, as well as obvious radiologically. In the acute stage,

a walking plaster gives most relief. At a later stage, a metatarsal pad and strapping support may suffice. In the tarsus, osteochondritis or avascular changes produced by trauma, may occur in the tarsal bones – e.g. Köhlers disease of the scaphoid – commonest in children aged 4–10 years. Epiphysis of the os calcis – Sever's disease – is commonest in boys aged 9–12 years. At the base of the 5th metatarsal, the classical 'dance fracture' may also be seen. Relief is obtained by immobilizing the foot in plaster with suitable padding for a few weeks, followed by exercises and physiotherapy.

Metatarsalgia occurs more commonly in females as the result of wearing faulty stockings and shoes, and it may well be associated with other foot disturbances such as pes cavus, arthritis and 'dance fracture'. Treatment by the fitting of correct footwear, incorporating a resilient support of felt or sponge rubber or a metatarsal bar in the shoe usually suffices with exercise therapy.

Plantar interdigital neuroma or neuritis and bursa produce severe sharp burning pain, usually in the region of the head of the metatarsal bone. This may have no relation to weight-bearing and makes the patient wish to remove the shoe. Tenderness on deep pressure over the third interspace and at times a palpable swelling are present. Conservative treatment with correctly fitting footwear and metatarsal support is frequently all that is required, but in obstinate cases resection of the neuroma is performed through either a plantar or dorsal incision in the arch of the toes.

Hallux valgus: Outward deviation of the big toe is usually associated with a bursitis or bunion and bone overgrowth on the medial side of the joint. Ætiological factors include heredity, faulty footwear and stockings, infection and injury. A morphological variation in the form of the reversion to a prehensile great toe may be present with a metatarsus atavicus. Symptomless hallux valgus is best left untreated, but all too frequently pain and the difficulty in fitting shoes make surgical correction necessary. A large number of surgical procedures have been described and they include arthroplasties, such as the Keller (1904) or Mayo (1908) operation, arthrodesis of the metatarsophalangeal joint, and osteotomy of the phalanx, metatarsal neck or base of the metatarsal and cuneiform. There are also sling operations – such as those of Joplin and McBride (1928) – inserting the adductor hallucis into the first metatarsal neck and also using a sling from the extensor of the little toe.

Hallux rigidus may result from trauma, osteoarthritis and rheumatoid arthritis, which is the most intractable form. The toe may be partially or completely rigid or limited in flexion or extension. Incomplete cases can be relieved by a proper shoe with metatarsal pad or bar. Occasionally manipulation and physiotherapy may help. Operative treatment is by arthroplasty or arthrodesis in the corrected position. Bunionettes may require excision in conjunction with hallux valgus and rigidus operations.

Hammer toes: This deformity results from contracture of the flexor tendons and may occur as an hereditary or congenital defect, from injury, arthritis or from improper footwear. A painful corn soon forms over the bony prominence and this may require resection in conjunction with spike arthrodesis. The second toe should never be amputated, but in the 5th toe such treatment is permissible, resecting part of the metatarsal including the head and neck of the bone. Spike arthrodesis or resection of the proximal phalanx are the methods most commonly used.

Painful heels may result from irritation by heel and counter of the shoe or from such systemic causes as rheumatoid and gonococcal fasciitis. Bone conditions include spurs and infection, which may be pyogenic or tuberculous.

Calcaneal spurs rarely require surgery, which may stimulate further bone reaction. Treatment of the systemic cause of the pain and corrective footwear usually suffice.

Bursitis may involve the bursa between the tendo achillis and posterior surface of the os calcis or an adventitious subcutaneous bursa at the tendo achillis insertion. Using shoes without counters or a heel pad or excision may be necessary. Injection with local anaesthetics, hyaluronidase and hydrocortisone may be useful in fasciitis.

Post-traumatic osteoporosis (Sudeck): This is characterized by severe pain, vasomotor changes in the foot and radiographic changes with irregular areas of 'mottling' in the acute cases, and more generalized changes when the condition is chronic. In very chronic cases taking years to recalcify, fusion of the tarsal bone may occur. Sympathetic nerve block may provide relief and also be used to confirm the advisability of sympathectomy, either periarterial or lumbar. It may also be used in conjunction with active exercise therapy, which is the initial line of treatment.

Arthritis of the foot: In both the rheumatoid and osteoarthritic forms, arthritis of the foot is not uncommon and results in pain, swelling, stiffness and deformity. Fore-, mid, and hind-foot may be involved and in acute cases rest in bed may be neces-

sary. In addition to general anti-arthritic measures, special local treatment includes various forms of physical therapy such as exercises, heat, massage, faradism and contrast and wax baths. The fitting of corrected footwear is important. Occasionally manipulation under anæsthesia may be helpful and surgery usually in the form of arthrodesis is indicated in the more severe cases. Gouty arthritis must always be kept in mind and treated accordingly, and Charcot's joints in tabes dorsalis and the neuropathic arthropathy in association with diabetes must not be overlooked. Foot pain may also result from peripheral vascular disorders such as thromboangiitis obliterans and arteriosclerosis, and skin disorders such as callus, corn, plantar wart and ingrowing toenail.

REFERENCES
Grice D S (1952) *J. Bone Jt. Surg.* **34A**, 927
Harris R I & Beath T (1948) *J. Bone Jt. Surg.* **30B**, 624
Hoke M (1931) *J. Bone Jt. Surg.* **13**, 773
Jones R (1897) *Lpool med.-chir. J.* **17**, 442
Keller W L (1904) *N. Y. med. J.* **80**, 741
McBride E D (1928) *J. Bone Jt. Surg.* **10**, 735
Mayo C H (1908) *Ann. Surg.* **48**, 300
Miller O L (1927) *J. Bone Jt. Surg.* **9**, 84

Mr M D England (*London*)

I would make a plea that, so far as 'sore feet' are concerned, doctors and chiropodists should have a greater measure of agreement on both the causes and the remedies. We have, after all, a common aim – to cure sore feet, or better still, to prevent them.

It is apparent that throughout the Country very many more patients with 'sore feet' find their way to chiropodists than to either orthopædic surgeons or to general practitioners and it follows that, on the whole, the patients in the chiropodists' surgeries reflect the truest picture of what causes the nation's 'sore feet', gross troubles excluded. An average chiropody practice will be made up of about 70% painful pressure lesions on the toes and plantar metatarsal area, verrucæ, conditions of the nails, the results of hallux valgus, and 'metatarsalgia' in its widest sense. The remaining 30% will be the results of severe deformity or systemic disease, with a fair proportion of children, and of pains in other parts of the foot, and with an increasing incidence of foot symptoms which are emotional in origin.

The following few suggestions are not merely my own opinions but are, in the main, widely accepted and supported. I have, however, deliberately concentrated on subjects on which doubts are frequently expressed, or on which sections of the medical profession or of the public frankly disagree with the main body of thought.

It is, I think, very significant that by far the majority of troubles arise in the fore-foot. Can we first agree that the health of the fore-foot – one might almost say of the foot – is very largely dependent on good toe function, and that the main reasons for the appalling incidence of minor foot troubles are (*a*) that this toe function has been lost or rendered ineffectual through bad footwear, or (*b*) probably much more important, that toe function is never really acquired at all because of a civilized environment. May I make a special plea for agreement on the developing foot: on babies' bootees, which are not only restrictive at the time when exercise of the toes is very desirable, but are all too often held on by a pink or blue tourniquet; on the desirability of children (and for that matter everybody) running around barefoot as much as possible, and on the risks of infection or trauma being slight indeed compared with the risk of permanent foot disorder. Also on the fact that young feet do *not* need support from the shoes (except perhaps when attached to an unusually heavy child), and that the lighter and more flexible the shoe the better; and on the fact that, in the absence of serious disorder, so-called 'weak ankles' in childhood are likely to be made worse rather than better by wearing boots. Additionally that human progress has produced for the foot, especially the growing foot, one of the greatest enemies of all, the crepe-stretch-nylon sock. If anything will inhibit toe function, these will. While we are considering children, may we combine to condemn the weekly ballet class for small girls at school – or more especially the shoes worn at it. If ballet must be learnt, it should be a whole-time job at a school such as Sadler's Wells, where the foot – as a part of the body and as a vital contributor to posture – receives a graduated training which gives it the best chance to survive the hazards of the most unnatural demands made upon it, during ballet dancing and in ballet shoes. May we also think again about the oft-recommended exercise of picking up a pencil with the toes. Though this may be useful in some cases of *retraction* of the toes, it is the worst possible thing for claw toes, since it exercises the very muscles which are already overworking and ignores those which are idle.

There is no such thing as a normal foot, any more than there is a 'normal' face; the criterion of a good foot should be that it serves its owner efficiently and painlessly, not that it is a particular shape. Therefore the expression 'flat foot' has less meaning than we thought in the pathological sense, and it is high time an alternative was accepted. The essential condition is one of rolling over, rather than flattening, of the longitudinal arch, and until a better title is agreed may we suggest 'valgus fore-foot'? Since quite a high proportion of cases of this condition in childhood are

the results of a supinated fore-foot, it is not logical to treat them with inside sole wedges, which tend to increase and perpetuate the supination and thus render it chronic. In suitable cases contra-wedging (i.e. lateral sole and medial heel) would seem preferable, while the inside sole wedge may be reserved to give relief to those cases – usually in later life – which are beyond correction.

Since faulty footwear is by far the greatest single cause of minor foot troubles, may we attempt agreement on what constitutes a 'good' or a 'bad' shoe? If freedom to develop is the most important thing for children, correct shoes are of paramount importance for the rest of life; and because this is almost entirely a female problem, may we concentrate on girls' and women's shoes to avoid complication. Basically, the criterion by which a shoe must be judged is – how is it held on the foot? Size and fitting apart, a shoe which is held on between the back of the heel and a grip on the toes is bad, while one which is held on across the dorsum of the foot by lace, bar or strap (and I do *not* include elastic) is potentially good. A grip on the toes, or a sliding forward in the shoe, not only causes pressure lesions, callus, corns and bursæ, but prevents proper toe function and is the enemy of foot health. It must therefore regretfully be said that all forms of court shoe are bad, and that the so-called casual shoe, which is virtually a court shoe with a low heel, must be included. However, one must be realistic about this because, whatever we say, women will continue to wear what is fashionable. As a compromise it would be reasonable to agree that court shoes (an expression which covers a multitude of sins) may be worn in the evening or for dress occasions, provided that healthy shoes are used for ordinary daily life. I would not, of course, make this concession to growing girls. I feel most strongly that it is essential for all branches of the medical profession and its ancillaries to be quite uncompromising about this. Court shoes of all types are bad for feet. and we should continually say so with one voice. To admit degrees of badness in this kind of shoe is wrong and certainly not helpful to the patient. On the other hand, our definition of a potentially good shoe allows a wide choice and includes types of shoe which are in some quarters quite unfairly stigmatized. For example, 'sling-backs' are not necessarily bad, provided the shoe or sandal is held on by an ankle strap or tarsal bar. One final point about footwear on which I should like to see agreement – although on the whole the shoe trade have improved children's shoes tremendously in the last twenty years, there is still room for improvement, especially concerning the so-called 'straight inner border'. Good, indeed *essential* as this is, it is not enough. It is most striking how a baby, standing barefooted, will abduct and firmly plantar-flex the great toe as a balancing mechanism. It is illogical to assume that this is a function which normally passes with childhood. This is one of the essential parts of foot-function and its almost automatic loss in civilized life, especially amongst women, is one of the great causes of fore-foot weakness and hallux valgus. Cannot we go that short step further and make room for an abducting big toe? It is amazing how a strong fore-foot, once acquired, will in later life resist the ravages of the most appalling footwear. The older I get, and the more feet I see, the more convinced I am that faulty footwear is by far the greatest cause of 'sore feet', and that one of the most pressing needs is to ensure that young feet have an opportunity to develop that full function which unfortunately many never do acquire in civilized life.

Meeting May 17 1961

A paper on **Co-operation Between the Hospital Service and General Practitioners** was read by Sir George Schuster (Oxford); it has been published in the *Practitioner* (1961) **187**, 92.

Section of Laryngology

President J H Otty FRCSED

Meeting March 3 1961

Discussion on Chronic Sinusitis in Childhood

Professor S D M Court (*Newcastle upon Tyne*)
The Origins of Chronic Sinusitis in Childhood

Recurrence and Chronicity in Respiratory Disease

Respiratory disease is the cause of two-thirds of the infective illness in Newcastle children in their first five years of life and in one form or another it is almost universal (Fig. 1) (Miller *et al.* 1960). There is also a tendency for respiratory illness to recur in the same child more often than it should by chance. In most children this tendency declines sharply after the eighth year (Fig 2).

Within this context of recurrent respiratory illness a minority, in our experience some 2% by the fourteenth year, will develop chronic respiratory disease. This composite term includes separately, or in various combinations, chronic sinusitis, bronchiectasis, allergic rhinitis, asthma and chronic bronchitis. When in our clinical work we face a child with a long-standing history of respiratory illness three questions naturally arise: Are we seeing recurrent or chronic disease? If recurrent, why do respiratory illnesses recur? If chronic disease, why in this particular child has chronicity developed?

In the present twilight of knowledge we cannot see the answers, but we can recognize some of the processes involved. An early illness may have caused such damage to the respiratory tract that it paved the way for the later ones or the child may have some personal susceptibility which made him especially vulnerable from an early age. The first process is seen in bronchiectasis following severe pneumonia or a foreign body in a bronchus. But in most cases we cannot relate the beginning of established disease to a single incident and the origins of chronicity are hidden in the mists of recurrence. Why then are the second group of children particularly vulnerable? In those with fibrocystic disease of the pancreas (mucoviscidosis) staphylococcal infection is rooted in abnormal respiratory mucus and this abnormality is genetically determined. In Kartagener's syndrome, situs inversus, chronic sinusitis and bronchiectasis, the genetic basis is accepted even if the nature of the defect is obscure. And children

Fig 1 *Newcastle upon Tyne, 1947–1952. The variety of illness in 847 children in their first five years.* (*Reproduced from Miller* et al. *1960, by kind permission*)

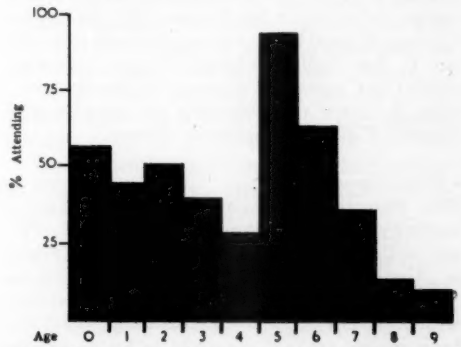

Fig 2 *The incidence of upper respiratory infections in 55 children in their first ten years.* (*Reproduced by kind permission of Dr John Fry*)

with allergic rhinitis or true asthma show an abnormal response of respiratory mucosa and muscle which is almost certainly genetically determined. But because personal susceptibility in these conditions is genetic we cannot assume that this is true for the majority of the group. Table 1, which shows in our Newcastle family study (Miller *et al.* 1960) the relationship of recurrent illness to the child's experience of respiratory infection in the first year, may contain a significant clue. A child with respiratory illness in the first year had significantly higher rates in the next four years than those who escaped, but it was immaterial whether the first-year illness was mild or severe.

Table 1
Newcastle upon Tyne 1947–52
Respiratory disease: recurrence in relation to experience in the first year
(from Miller *et al.* 1960)

First-year respiratory illnesses	*No. of children*	*Mean attacks in the next four years*				
		2nd	*3rd*	*4th*	*5th*	*Total*
Severe	205	0·94	1·11	0·86	0·86	3·77
Mild	297	0·94	1·17	0·90	0·80	3·81
None	345	0·64	0·97	0·81	0·61	3·03

This makes it clear that the recurrent respiratory disease in these children is not the sequel to a severe initial illness. What then is the nature of their excessive susceptibility? This may be due to genetically determined abnormalities of the respiratory tract of which we are still ignorant. It is possible too that recurrence is the expression of resident respiratory virus infection with intermittent clinical illness as with herpes simplex. On the other hand respiratory infection early in the first year may produce an altered immunological response rather than structural damage; a response expressed in susceptibility to recurrence and chronicity rather than as in most children by increasing immunity and resistance. This is at present no more than a hypothesis but in view of the special responses to infection which are known to occur in fœtal life and early childhood it should not be too readily set aside. It suggests that we should pay particular attention to the first year both for better understanding and possible prevention of chronic respiratory disease.

Chronic Sinusitis

But, whatever the mechanisms, they lead in a minority of children to persisting disease. The particular expression with which we are concerned is chronic sinusitis and we would define this as 'a state of continuing upper respiratory infection with persistent purulent nasal discharge which has been present for twelve months or longer and in which pus was present on proof puncture in the maxillary antra'.

This is a stringent definition and not satisfactory for optimum treatment. We used it deliberately to define a group of children to whom the term unquestionably applied. The recognition and management of chronic sinusitis in this sense in a hundred children will be described in the paper which follows (p 665). Twenty-five were studied jointly by Mr Black and myself. They have been seen regularly for an average period of four years and in addition to clinical assessment of nose, ears and chest we have measured the bacteriology of the nasal discharge and the eosinophil levels in the blood, taken plain films of the chest and, where necessary, bronchograms, and carried out simple spirometry. We have found elsewhere that the forced expiratory volume in one second (FEV 1·0) and its percentage relation to the forced vital capacity (FEV%) are reliable indices of pulmonary ventilatory capacity. This is notably impaired in asthma, the impairment sometimes persisting between attacks when the child is considered well; impairment of a lesser degree is found in some children with chronic infective disease and suggests widespread bronchitis (Strang & Court 1960). By this combined assessment these 25 children who had initially been regarded as 'essentially sinusitis' were more correctly placed in the categories set out in Table 2.

Table 2
The final assessment of 25 children regarded initially as chronic nasal sinusitis

Sinusitis	8
Sinusitis and bronchitis	6
Sinusitis and bronchiectasis	9
Allergic rhinitis-sinusitis	2

In 4 out of 5 children the condition appeared to start during the first three years of life, most commonly in the first year. Chronic respiratory suppuration can be confined to the nasal sinuses but it is generally associated with disease in the lower respiratory tract. This, however, is often intermittent and not associated with impaired pulmonary ventilation. Impaired ventilatory capacity was found in only 2 of the 25 children: the first an asthmatic with chronic sinusitis superimposed on allergic rhinitis, and the second a girl with chronic sinusitis and bronchiectasis. The tests of ventilatory function in this child suggest that her apparently localized bronchiectasis is associated with a more diffuse bronchitis.

The contribution of allergic rhinitis to chronic sinusitis is not easy to determine and the incidence (8%) in these 25 children may be an underestimate. Our 2 children had in addition to the clinical features of an 'itchy stuffy nose' and excessive sneezing, intermittent wheezing and blood eosinophil counts greater than 600/c.mm (Strang 1960).

The children with chronic sinusitis and bronchiectasis will not be considered here except to stress the value of plain radiographs at intervals of several months; persisting shadows in the same site both confirm the existence of established disease and in some cases are a more useful measure of the amount of lung involved than bronchography.

These observations emphasize once again that the respiratory tract is a single tract and that in whatever sector disease appears the tract must be investigated and treated as a whole. They remind us too that the origins of chronic disabling disease are in the first three years of life, particularly the first. This is ancient counsel but the division of medical care between family doctors, pædiatricians in hospital and in the child welfare and school health services, chest physicians and E.N.T. surgeons, still lead to continuing failure in its application.

REFERENCES
Miller F J W, Court S D M, Walton W S & Knox E G (1960) Growing up in Newcastle upon Tyne. London; p 12
Strang L B (1960) *Brit. med. J.* i, 167
Strang L B & Court S D M (1960) *Postgrad. med. J.* 36, 276

Mr J I Munro Black (*Newcastle upon Tyne*)

Chronic Sinusitis in Children

The information and opinions presented in this paper are derived from the study of 100 children who had chronic sinusitis when I first saw them. To be sure that they all had real sinusitis as defined for the purpose of this discussion, only those have been included who were found, by puncture and lavage, to have pus present in their maxillary antra.

All children were seen personally after reference by another medical colleague, either a general practitioner, welfare medical officer or pædiatrician. The reasons for seeking further consultation fell broadly into four groups:

(1) Longstanding recurring or continuous upper respiratory tract infections: 42 cases.
(2) Longstanding recurring or continuous bronchial infections: 26 cases.
(3) For possible removal of tonsils and adenoids: 14 cases.
(4) Otorrhœa resistant to treatment by general antibiotics: 18 cases.

Ages: When first seen by myself, 71 of the children were aged between 5 and 10 years, only 11 under 5, the youngest being 3, and the remaining 18 up to 14 years old.

Sex: There were 57 girls and 43 boys.

History: There has been some variation in the approach to history taking, whether information was sought for enquiry purposes or just as routine case management. One smaller group was segregated for study by Professor Court and myself, and in each separate case a very full history obtained. This proved to be a most time-consuming exercise and revealed the prolonged nature of the complaint and the surprising amount of trouble caused over the years. The children's mothers revealed extraordinary memories and dated the beginning of trouble right back to the early years of life – often in the first year. Commonly the trouble had begun with a general respiratory infection, perhaps as serious as pneumonia, sometimes as specific as whooping cough or pink disease, and then persisted as variable catarrh ever afterwards. Usually the mothers agreed that catarrh meant moisture and not just obstruction, although nasal obstruction was often mentioned as well. It was reassuring to find the mothers definite in their opinions that their babies had had some respiratory abnormality at a very young age, but disappointing to hear that when medical advice was sought they had so often been reassured that there need not be any anxiety, and that the child would just grow out of it.

Of course, many practitioners had sought further opinion, but often without anything of real help being offered. There was then a tendency to seek other advice and the children were found to have attended several specialists, often receiving independent treatment from them at the same time, and without each other's knowledge. Some of the children under the care of a general practitioner or pædiatrician had had long-term supportive treatment by daily penicillin or twice weekly broad-spectrum antibiotic. Often coupled with this were daily postural coughing and breathing exercises. The hopeful initial prescription of nasal drops was very common, and frequently continued for long periods. Some had had their tonsils and adenoids removed as well, but no consideration given to the presence of sinusitis, and occasionally treatment had been given for wax keratosis only. They all still had their chronic sinusitis.

Very frequently these children had been treated for acute exacerbations of respiratory infections as isolated incidents.

These voluminous case histories were not of real value to the individual patient as regards treatment, but did serve to reveal a life of prolonged chronic invalidism, and the hope that something could be done to improve matters. The great importance was for ætiology and as a study of social and administrative medicine.

The stories revealed a surprising medical

ignorance regarding sinusitis and the need for further study and teaching. This must be pursued but probably will have to be done with small groups of patients owing to the time required for each patient.

Examination: The physical examination of the child as far as I am concerned has been in the first place very simple, the reason being that I hoped to demonstrate abnormalities by easy methods which anyone could emulate. The child was asked to blow his nose into a dish, and perhaps thus produce and demonstrate mucopus – which usually justified a diagnosis of sinusitis. Then the nostrils were examined with the aid of a headlamp or mirror and probably showed pooling of mucopus, but often little abnormality was visible. The posterior pharyngeal wall was looked at through the open mouth, and often revealed sticky pus coming down from the nasopharynx – again most suggestive of sinusitis. The ears were examined especially for the presence of wax keratosis or suppuration. Finally, the child was asked to cough, or failing this to perform deep inspiration and forced expiration. In the cases discussed this usually revealed the presence of moisture. The productive cough of these children was very obvious, and surprisingly frequently had been previously ignored.

Signs and symptoms: The signs and symptoms which to me suggest the presence of chronic sinusitis are:

(1) Upper respiratory catarrh – mucopus in the nose or on the posterior pharyngeal wall.
(2) A productive cough – a history of recurring bronchitis.
(3) Wax keratosis in the ear or suppuration therefrom.

Fifty of these children did have wax keratosis which justified examination under general anæsthesia. I have not had X-ray examination of the paranasal sinuses because I believe clinical history and ordinary examination is enough to justify a likely diagnosis of chronic sinusitis. The only way of being quite sure is by antral puncture and lavage. Similarly I have not bothered with an X-ray of the chest, although when referred by a pædiatrician they will already have had this done. I believe there is a danger of false confidence being caused in that the X-ray picture may be normal and yet bronchial suppuration be present. I have known this normal X-ray appearance to be used as false assurance to a justifiably anxious parent.

I must stress that the chest should not be passed as ultimately normal without X-ray examination as well.

The real necessity is to look at the whole respiratory tract as one, and not accept separation of it into upper and lower entities.

Examination under anæsthesia: All these present children were then examined under general anæsthesia:

(1) The ears were examined with the help of good illumination but without magnification, and cleared out if necessary by probe, hook, forceps and sucker – often a difficult and tedious performance.
(2) Bilateral antral puncture and lavage was performed, the pus obtained being sent for bacteriological examination.
(3) The postnasal space was examined digitally, and any large adenoid mass removed.
(4) Some written record was made of the presence or otherwise of pus in the lower respiratory tract.

Nothing further was done at this stage regarding any bronchial infection.

Bacteriology: Almost universally the report was of the presence of *H. influenzæ* and/or pneumococci. It will be realized that the demonstration of these organisms required special culture technique, but when looked for they were found.

Treatment: The principle of treatment adopted was to attempt removal of the infecting organisms by killing them *in situ* and hope that the damaged respiratory mucosa could then return to normal. No attempt has yet been made to carry out more controlled trials of forms of treatment. In view of the bacteriological findings the antibiotic selected for this purpose was Aureomycin, and it was given by mouth in full dosage appropriate to the age of the patient and for convenience in periods of one week. To check progress further examination under general anæsthesia by antral lavage was carried out. Gradually I formed the opinion that if antibiotic alone was to cure the sinusitis then it would do so in two weeks or so.

The criterion of cure was first and foremost a dry respiratory tract – no moist sounds on coughing or forced expiration; no mucopus present in the maxillary antra to puncture and washout, although in some later cases I accepted a dry upper respiratory tract as cure without trying to prove this by antral lavage. Of course, the ears must become normal as well, realizing that old scarring may have produced some deafness. When these children are followed up afterwards, as they must be, and by the individual who has treated them, there is little doubt which are quite well, which improved and which little or no better. In this case, the mothers have not proved so reliable in their estimate of their children's condition. Their

opinions have often been too hopefully optimistic.

Failing apparent cure after two to six weeks on a broad-spectrum antibiotic, I have performed bilateral intranasal antrostomy and continued the antibiotic for at least another two weeks. If still not cured then, I have for the moment not offered anything further.

Of the 100 cases treated: 46 had Aureomycin only; 54 required antrostomies as well.

Most of the failures have had notable bronchial suppuration, which was of course fully investigated, but in some cases it was thought that the chronic sinusitis was the major lesion resistant to treatment. Those patients who failed to respond to treatment will be studied further as a special group. Some cases were excluded initially from further study because they appeared to have such hopeless bronchial suppuration that it was considered a waste of time attempting treatment for the co-existent chronic sinusitis.

Prognosis after treatment: I have learnt to be very cautious about assessing the results of treatment because, even when apparently well, these children relapse so easily. It is reassuring at times to observe them have a common cold and not relapse to suppuration, but if they do so the appropriate antibiotic will dry them up if they really have been well. It may need two weeks or more of treatment to do this.

Bearing this in mind, the results of treatment to the hundred cases were:

Apparently cured	50
Improved	23
Not really helped	27

These results are better than was anticipated, the whole picture being coloured by the residual failures who seem to be ever with us.

The present position regarding treatment: I now believe it is possible to accept a diagnosis of chronic sinusitis on clinical history and simple examination alone. This justifies a trial of up to two or four weeks with a broad-spectrum antibiotic. If not then apparently well, examination under general anæsthesia is required. When first examined, if wax is seen in the ears it must be removed, and of course general anæsthesia may be required – this is because probably half of the children will be cured as regards their sinusitis, but may be left with a wax keratosis which will continue to cause destruction of the deep auditory canal. Bearing this in mind, a general practitioner can begin treatment and may be successful without needing further help. There must, however, be no doubt at all that the child is well, and it is far better to seek consultant advice than allow the child to suffer irreparable damage.

Ætiology: The question of ætiology is important because it should be possible to prevent chronic sinusitis from occurring. First and foremost, any acute respiratory infection in a child must be seen to get better or be cured. Many of these children seemed to start their respiratory suppuration as babies and were noted to be abnormal by their mothers, and this must not be ignored by general practitioners. Also, general practitioners must be made to feel that these cases are welcomed by specialists and not shunned. Most industrial communities contain many such infected babies and they must not be allowed to grow up handicapped by chronic sinusitis. It is, I believe, in these very young children that removal of an adenoid mass may be most helpful.

Since treatment of the established case of chronic sinusitis is so difficult and the results so unsatisfactory, it is clear that all efforts must be made towards prevention.

Principles Involved in the Prevention of Chronic Sinusitis

(1) The condition begins very early in life, even in the first year.
(2) Any severe cold with purulent nasal discharge in a child of any age must not be allowed to persist untreated. General antibiotics must be be given until the child is better or referred for further opinion.
(3) Nasal obstruction in the very young child must not be neglected.
(4) Further education is necessary for students, general practitioners and pædiatricians.

Mr J Crooks (*London*)

Sinusitis in children is very common – I cannot give percentage incidence figures like the opening speakers for I can only record my experience at Great Ormond Street, and in private practice, and the patients come from almost anywhere. No doubt I see an undue proportion of sinusitis because doctors know that it is a special interest of mine. Suffice it to say that in 1947, 750 children came to the hospital department with X-rays showing opacity of the sinuses, and out of these, 340 were found to have mucopus by proof puncture. Ever since I took an interest in this subject and drew attention to it by a paper in 1936 we have had to maintain a special antrum wash clinic, and the weekly attendances in 1959 averaged 24. Of these children over half were under 7 years of age.

It is difficult to make an exact definition of chronic sinusitis. I would call sinusitis acute during a cold or upper respiratory infection, subacute if nasal discharge from the sinuses persisted for two months, and after that I would regard it as chronic. Most of the children attending the antrum wash clinic are chronic in that sense.

The importance of sinusitis is still not sufficiently recognized. Before 1936 at Great Ormond Street anything wrong with the nose and throat was labelled 'tonsils and adenoids' and nobody looked any further. But now I think we always suspect sinusitis in any child with predominantly nasal symptoms and persistent or recurrent lung or ear infections.

The natural history of chronic upper respiratory infection in a child seems to be as follows: The first thing a child gets is a cold, and he gets a succession of colds if the modern welfare state provides him with a day nursery or infants' school which he can attend when he is 2 or 3 years of age and so enable his mother to go out to work. Young children thrown together at this age get cold upon cold from each other and no one in the nursery has time to teach them to blow their noses. It is at this time that the sinus mucosa and the lining of the nose become chronically inflamed and congested and discharging. The child sniffs back the discharge which lies over the adenoids and causes them to hypertrophy. Then he has to breathe through his mouth and the tonsils get the brunt of the inspired infection. The lungs are irritated by taking in unfiltered and cold air. At the age of 5 or 6 he has to have his tonsils and adenoids removed and may have chronic sinusitis as well.

Prevention is better than cure. Young children should not be subjected to repeated infection from their schoolmates by going to school as a social convenience at the age of 2 or 3 or 4 when they have not developed any immunity. They must be taught to blow their noses and should do so by the age of 2½ and they must breathe properly through them and keep their mouths shut. If a child has developed a chronic stuffy or snuffly nose he should be kept away from school and given shrinking nasal drops and his mother must concentrate on the proper use and blowing of his nose. This may be the time to have an X-ray film made of the nasal accessory sinuses and assess the size of the adenoids. If the child goes on with an unsatisfactory nose he has reached the stage when chronic sinusitis is establishing itself. The child will have had cold upon cold all winter and he will not be free from discharge between colds and X-ray films will show that one or both antra are dull. We find it easier to diagnose and treat antrum infections than those in other sinuses, which are not nearly so frequent.

These early chronic antrum infections, if the children cannot have the benefit of a prolonged holiday in a good climate with proper food and environment and instruction in nose-blowing and breathing, must be treated by lavage and will usually clear up after a few washes. In my opinion, lavage is the essential element in the treatment of sinusitis. The antrum remains infected because of its poor design relative to our upright position and the trouble is a mechanical one. Its opening is small and high up like a ventilator to a room instead of a decent door at floor level. During a cold it fills up with mucopus just as does the nose. But the nose recovers quickly because the discharge is blown down or sniffed back but the antrum goes on retaining its discharge which lies in it like a cesspool. Only when it is full up or the head changes position does some discharge get out of the overflow pipe which is the ostium. The lining membrane of the sinus becomes sodden and œdematous and possibly polypoid and fibrosed and the cilia are rendered impotent by the weight of mucopus lying upon them. This mechanical aspect is more important than the persistence of infection and indeed the mucopus washed out from many of these sinuses gives no growth on culture. But if the cavity is repeatedly spring-cleaned by lavage the membrane has a chance to recover its normal health and the cilia to work again and sweep any discharge out of the cavity and through the ostium into the nose. Practically all sinusitis is curable if taken in time and treated by lavage together with proper general measures. I am not impressed by the efficacy of antibiotics or other drugs given systemically or by leaving them in the sinuses after lavage.

If the opportunity is lost because the diagnosis is not made early enough or the lavage is not carried out as often as is necessary, other measures may have to be used but they are unsatisfactory and a confession of failure. Antrostomy makes an opening low down in the antrum but the cilia work away from it rather than towards it and the opening closes up within a few weeks or months because the child's bone grows so quickly. Anyway, a young child does not find it possible to wash his own antrum out with an antrostomy cannula and very few mothers are prepared to do this. When the antrostomy has closed the child is worse off than ever because he has a scar in his nasal and sinus mucosa which will interrupt the continuity of the ciliary field and the protective sheet of mucus. The more radical procedure of removing the lining membrane by the Caldwell-Luc operation makes one hesitate a good deal. There is not much room in the child between the unerupted teeth and the nerves and vessels to the upper teeth and in my hands the antrum does not again become lined by a satisfactory ciliated mucous membrane. Some people insert polythene tubes into the antrum and wash through these but this is not a good substitute for lavage because the child has to be kept in hospital which is the worst thing for anybody with a chronic respiratory infection. He cannot very well go out and about with tubes sticking out of his nose, and

anyway, the tubes act as an irritant in the nose and the sinuses.

It seems to me essential that sinusitis should be diagnosed early and treated by repeated puncture-lavage and general measures until it is cured. Given the proper set-up and patience and experience with children, it is perfectly possible to go on washing the sinuses of young children every week under local anæsthesia, and this is what I do. It is neither desirable nor practicable to give them a general anæsthetic once a week. I have very few failures – only 10 out of 100 consecutive children in 1959 and they had had sinusitis for a very long time before they started treatment. Most of the antra are clear after three or four washes but in some I have had complete success after fifteen weekly washes combined with general measures to improve their environment. The children I remember best are, naturally enough, my private patients upon whom I have done all the treatment myself and who become good friends of mine after we have seen each other so often.

REFERENCE
Crooks J (1936) *Arch. Dis. Childh.* **11**, 281

Mr H V Forster (*Liverpool*) said he had been grateful to hear Mr Crooks' reference to social and economic conditions affecting the natural development of a certain degree of immunity in the home.

There appeared to be much demand for admission to the day nurseries of the Local Authority, and in families where home conditions were normal yet difficult the child was sent in due time to a nursery school, many of them run privately. The problem, however, did not end even in the boarding school, but it was not quite the same, and Dr Alison Glover had once reminded him about complications from the secondary invading organisms.

Primary upper respiratory infections including the exanthemata were of equal incidence in boys' and in girls' schools, but the secondary invaders were not so likely to trouble the girls, because it had long been the custom to offer greater privacy, by screening, in their dormitories.

Mr J I Munro Black, in reply, said he had no definite views as to whether it was better to clear the nose by blowing or, as perhaps must be admitted is more natural, by sniffing. The important point was that some children neither blew nor sniffed, and thus allowed pooling in the nostrils. An attempt must be made to find out why this occurs. Plenty of children were seen in the older age groups who have been allowed to become permanent habit mouth-breathers, perhaps transformed to this from the natural habit of nose-breathing by some pathological disturbance, which should, of course, have been attended to many years previously.

He said that the reason for using a systemic antibiotic as a form of treatment was partly as already stated in his paper, but also in the hope that if it proved efficacious it would be something that could be used by general practitioners. It was only of limited help offering treatment such as repeated antral puncture and lavage, or indwelling polythene tubes, which must be carried out by a specialist and required hospital visits.

All cases treated had been followed up for some years afterwards to note results. Future efforts would be towards earlier treatment in the very young age groups, in the hope that the established chronic suppuration would be prevented, and ultimately it was hoped that this would be by general practitioners so that attendance at hospital for specialist help would become unnecessary.

Meeting February 3 1961

A Discussion was held on **Recent Advances in the Treatment of Intrinsic Carcinoma of the Larynx;** the opening speakers were Mr C P Wilson, Mr R S Lewis and Dr Frank Ellis.

The following also took part in the discussion: Dr I Simson Hall, Mr B S Jones, Miss M D Snelling, Mr F C W Capps, Dr F Roth, Mr R G Macbeth, Professor V F Lambert, Mr H J Shaw, Mr R D Owen, Mr J C Hogg and Mr J C McFarland.

The meeting will be reported in the *Journal of Laryngology.*

Meeting May 5 1961

A Discussion was held on **Vasomotor Rhinitis;** the opening speakers were Mr A Young, Dr Miles Taylor and Mr P H Golding-Wood.

The subsequent discussion was opened by Mr J Angell James and the following also contributed:
Dr Douglas Ranger, Mr G G Mowat, Mr H Zalin and Mr H V Forster.
Mr Golding-Wood replied.

The meeting will be reported in the *Journal of Laryngology.*

Books recently presented and placed in the Society's library

(*Continued from p. 656*)

Krømer H
Bone homografts in the surgical treatment of cysts of the jaws and periodontal tissue: a clinical and experimental study
pp 121
Oslo: University Press 1960

Ludovici L J
Cone of oblivion: a vendetta in science
pp 224 25s
London: Parrish 1961

Lyman C P & Dawe A R *eds.*
Mammalian hibernation. Proceedings of the I International Symposium on natural mammalian hibernation
(*Bull. Mus. comp. Zool. Harv.* Vol. *124*)
pp 549
Cambridge, Mass.: Museum of Comparative Zoology 1960

Ministry of Labour (& National Service) & Central Office of Information
Health at work: a description of medical services in fourteen British factories
pp 76
London: Ministry of Labour 1961

Parhon C I, Balaceanu M & Albu N
Endocrinologie embrionară
pp 213
Bucuresti: Editura Academiei Republicii Populare Romine 1960

Quattrin N, Dini E & Palumbo E
Leucemie basofile
pp 233 L 2,500
Pisa: Edizioni 'Omnia Medica' 1959

Rashevsky N
Mathematical biophysics: physico-mathematical foundations of biology
3rd ed 2 vols. $5
New York: Dover Publications 1960

Rome. Università. Istituto di Storia della Medicina
Catalogo delle opere contenute nella biblioteca
Vol. I. A–B pp 377
Roma: Istituto di Storia della Medicina 1960

Royal College of Surgeons of England
The history of the College Council Club 1869–1958
Edited by Sir Ernest Finch
pp 85
London: Royal College of Surgeons of England 1960

Samuels J
Kanker en hormonen
2nd ed pp 96
Hoorn: West-Friesland 1961

Scandinavian Summer Meeting of Biochemistry, Medicinal Chemistry, Pharmacology and Physiology
2nd Meeting [being] Joint Meeting with the Biochemical Society
Turku August 27–29 1959
pp 121
1959

Schwann T
Lettres de Theodore Schwann. Editées et annotées par Marcel Florkin
pp 274 Fr. 250
Liège: Société Royale des Sciences de Liège 1961

Senator H & Kaminer S G eds.
Krankheiten und Ehe. Darstellung der Beziehungen zwischen Gesundheits-Störgungen und Ehegemeinschaft
pp 857
München: Lehmann 1904

Shelly Hernandez R de
La estadística aplicada a las ciencias biológicas
pp 623
Caracas: Editora Grafos 1959

Societa Italiana di Oftalmologia
Symposium sul tema 'Cura dello strabismo' Coordinatore: G B Bietti. XLIII Congresso 6–9 Ott. 1957, Milano
pp 285
Roma: Arte della Stampa 1957

Still G F
The history of pædiatrics: the progress of the study of diseases of children up to the end of the 18th century
pp 526
London: Oxford University Press 1931

Thorek M
Surgical errors and safeguards
5th ed pp 652 £10
London: Pitman 1960

Weber F Parkes
Miscellaneous notes
Series 10 & 11
pp 7+7
London: Lewis 1961

World Health Organization. Regional Office for Europe
The prevention of accidents in childhood
pp 224
Copenhagen: WHO Regional Office Europe 1960

Imperati L & Tommaseo T
Chirurgia delle arterie mesenteriche
pp 195 L 4800
Roma: Edizioni Mediche e Scientifiche 1960

Section of Psychiatry

President Noel Harris MD

Meeting January 10 1961

Discussion on Implications of Recent Genetic Research in Psychiatry [*Abridged*]

Professor L S Penrose (*London*)

Recent researches have made use of new techniques in two main fields, the biochemical and the cytological.

BIOCHEMICAL ADVANCES

By means of methods such as chromatography and electrophoresis, the detection of genic effects has become much more exact than formerly. This is shown in the study of abnormal metabolites, sex hormones, enzymes and other proteins. By such means the pathological effects of single gene or single locus changes (mutations) are identified.

Much rather unproductive biochemical research in mental disease has been concerned with secondary pathological changes, not directed at finding primary inborn errors such as complete or partial enzyme blocks. These can cause (*a*) *mental defects*, if the error induces developmental failure, or (*b*) *mental illness*, if the effects are cumulative or toxic.

Specific examples are phenylketonuria and Wilson's disease. Alzheimer's disease, Huntington's chorea and also schizophrenia of some types are soon likely to be added to the list.

CYTOLOGICAL ADVANCES

General

The mutant genes which are concerned with specific biochemical errors cannot yet be seen or even located on the chromosomes. However, methods now available have enabled the chromosomes themselves to be made clearly visible and classifiable. Furthermore, many gross abnormalities associated with recognizable defects can be clearly defined.

The normal set of 22 autosomes and the pair of sex chromosomes (XY in the male and XX in the female) can be fairly easily seen in dividing somatic cells derived from bone marrow, peripheral blood, epithelial tissue or connective tissue (cultured for periods from a few hours to many months).

Anomalies of chromosome *number* (polyploidy and aneuploidy) and of chromosome *structure* have been studied in experimental animals and plants for half a century. Polyploidy and haploidy can be normal in animals and plants; haploidy (23) is normal in gametes, sperms and ova; tetraploid cells (92) probably occur normally in the liver; triploid cells (69) occur in long-standing cultures and have been reported in a skin culture from a retarded child.

One well-known kind of aberration is a mechanical error called 'non-disjunction' – one or more chromosomes slip into the wrong daughter cell at the time of division. The result is an uneven arrangement called aneuploidy. This occurs most often in germ cell maturation and is attributed to failure, in the early stages, of the normal alignment of homologous chromosome pairs. Numerical anomalies in chromosomes lead to so-called 'dosage effects' in the organism: there is lack of balance among proteins and electrolytes rather than the presence of specific unusual metabolites such as occurs in consequence of gene mutations. Aneuploidy in plants is well tolerated but in animals it seems to cause serious disturbances of growth.

Anomalies of chromosome structure are attributed initially to breakages. These may lead to almost any type of defect in the organism according to whether genes are lost by deletion of segments or duplicated after disturbed cell division. Natural variations of chromosome morphology are possible within a species. Examples of all these peculiarities have now been found in man.

Special

(*a*) *Sex chromosomes:* Many years ago, Mott (1919) observed that in some types of schizophrenia there was gonadal atrophy. We now know that mental retardation and paranoid states occur in Klinefelter's syndrome, in which gonadal agenesis is associated with the presence of an extra X chromosome. In some other types of patient the Y chromosome shows peculiarities.

(*b*) *Autosomes:* Among abnormalities of the autosomes, the findings in mongolism are of the greatest interest both genetically and psychiatrically. As first shown by Lejeune *et al.* (1959), the standard peculiarity is an extra small chromosome (probably a No. 21) present in all somatic cells. This usually arises by non-disjunction during gametogenesis and it is most likely to arise in the ova of elderly mothers. The specific mentality of the mongol patient has many similarities to psychosis (i.e. defect in abstract reasoning, relative verbal facility, catatonia).

It is genetically insufficient to assume a chance origin of chromosome aberrations. There are hints that satellited chromosomes (Nos. 13, 14, 15, 21 and 22) are subject to special mechanical difficulties in cell division. Another parallel autosomal aberration affects one of the group Nos. 13, 14, 15, as first shown by Patau *et al.* (1960), producing a rare defect – cleft palate, polydactyly and coloboma. As in drosophila, there are probably genes which predispose the parent to produce many types of abnormal gametes. Mongolism and Klinefelter syndrome can be combined in the same individual. Mongolism is common enough for some specific causes to be sorted out. Maternal age is the critical factor only in three-quarters of the cases. In the rest parental age is not a factor and there is hereditary disposition. There will be secondary non-disjunction if a parent is affected. There may be an invisible genetical predisposition in some unaffected parents. A centric fusion (translocation) can lead, either immediately or after some generations, to unbalance of the critical chromosomes. It seems probable that these centric fusions depend on the structure and function of the satellited chromosomes.

REFERENCES
Lejeune J, Gautier M & Turpin R (1959) *C. R. Acad. Sci., Paris* **248**, 1721
Mott F W (1919) *Brit. med. J.* ii, 655
Patau K, Smith D W, Therman E, Inhorn S L & Wagner H P (1960) *Lancet* i, 790

Professor Paul E Polani (*London*)

Sex Chromosome Aberrations in Relation to Neuropsychiatry

Chromosome anomalies exist in two *clinical* sex abnormalities and their variants: (1) Ovarian dysgenesis. (2) Klinefelter's syndrome.

The third condition in which sex chromosome anomalies exist, the triplo-X female, does not usually present as an abnormality of sex.

It is important to remember that nuclear sexing is not only essential as a routine diagnostic procedure but also for the correct interpretation of the chromosome findings. It is most easily carried out on cells scraped off the oral mucosa. With suitable staining and examination under the light microscope it can be seen that 20–40% of the nuclei of the oral mucosal cells of normal females contain a single chromatin mass at the nuclear membrane. This mass indicates the presence of two X chromosomes though it is probably formed by only one of them. In normal males, in whom only one X chromosome is present, the sex chromatin is generally absent. In addition to determining the proportion of cells containing the sex-chromatin masses, the size and number of the masses are estimated. It has been found that there are as many X chromosomes present as there are sex-chromatin masses plus one. The presence of small masses in addition to normal ones indicates the presence of extra, fragmented, X chromosomes.

The Chromosomes in Ovarian Dysgenesis

The essential feature of this condition is primary gonadal maldevelopment: no ovaries are found, but only 'streaks' of connective tissue usually devoid of follicles. As a consequence women with ovarian dysgenesis have primary amenorrhœa and lack other secondary sex characters. Commonly there are associated abnormalities and there is always shortness of stature. In a large proportion of patients other somatic anomalies are present such as coarctation of the aorta, renal anomalies and usually webbing of the neck. Some authors use the eponym Turner's syndrome for patients with neck webbing. When stature is normal but there is evidence of gonadal maldevelopment, as in ovarian dysgenesis, the name of 'pure gonadal dysgenesis' is used.

Most patients with ovarian dysgenesis are chromatin negative on nuclear sexing. The chromosome findings of at least 30 chromatin-negative patients with ovarian dysgenesis have been reported (for review *see* Polani 1961). Almost invariably the chromosome number is 45 and a single X chromosome is present, a finding referred to as XO. Although the X chromosome cannot be identified in a positive manner there are good reasons for believing that only one X chromosome is present because: (1) These patients have a sex anomaly, (2) they are chromatin negative as are normal males, and (3) they have the high incidence of red/green sex-linked recessive colour blindness of normal males.

Chromatin-positive cases with ovarian dysgenesis are rarer, but two chromosomally distinct

sub-groups have been identified. The first is the mosaic group. In this group the chromosome counts yield a bi-modal number. Careful analysis of the distinct populations of cells with 45 and with 46 chromosomes reveals respectively an XO and XX sex chromosome constitution. This finding suggests that the tissues from which the cell cultures were made consist of two distinct populations of cells and consequently that the patients are chromosome mosaics. This form of mosaicism presumably arises from an error of partitioning of chromosomes in the course of somatic cell division. The error may occur during early embryogenesis or later. The original zygote in which the chromosome error occurred may be normal or abnormal.

The second group of chromatin-positive ovarian dysgenesis is different. These patients have 46 chromosomes: there is a single X chromosome, but there are three instead of two chromosomes corresponding to chromosome No. 3. Because of the chromatin-positive results of nuclear sexing it is thought that one of these three No. 3 chromosomes is in fact a so-called 'isochromosome' of the long arm of the X chromosome (Fraccaro, Ikkos, Lindsten, Luft & Kaijser 1960). These isochromosomes are thought to arise as a result of a misdivision of ordinary chromosomes: their centromere splits transversely instead of longitudinally.

The frequency of chromatin-negative ovarian dysgenesis is unknown but it appears to be of the order of 1 in 5,000 to 1 in 10,000 women. In hospital series, among chromatin-negative patients with ovarian dysgenesis who have webbing of the neck, the frequency of intellectual subnormality, usually not grave, is about 1 in 7. Among those who have no webbing of the neck the incidence is approximately 1 in 20.

The Chromosomes in Klinefelter's Syndrome

The essential clinical feature of Klinefelter's syndrome is the presence of small testes after puberty. Gynæcomastia and other hormonal disturbances are often found. Azoospermia is probably universal and the histological findings of the testis are quite characteristic. Most males with Klinefelter's syndrome are chromatin positive. Among these the majority have a single mass in their oral mucosal cells but a few have been described with two masses and even one with three.

The findings have been reported in about 30 chromatin-positive males with Klinefelter's syndrome with a single sex chromatin mass in the cells of the oral mucosa. In the majority of them a uni-modal distribution of chromosome counts was found. The cells contained 47 chromosomes: the sex-chromosome constitution was interpreted as XXY. Various facts support this interpretation – the presence of a sex anomaly, the chromatin positivity on nuclear sexing and the low frequency of sex-linked recessive red/green colour blindness in this group of males.

A number of patients with chromatin-positive Klinefelter's syndrome have been described in whom the chromosome counts were bi-modal: there were cells with 46 and others with 47 chromosomes. Analysis of these cells revealed an XX sex-chromosome constitution in those with 46 chromosomes and XXY in those with 47. Four patients have been described with chromatin-positive cells with double sex-chromatin masses, small testes, and severe intellectual subnormality. In these, a chromosome count of 48 was obtained and, in view of the nuclear sexing findings, the sex-chromosome constitution was thought to be XXXY (Ferguson-Smith *et al.* 1960). Finally, a little boy was reported with ambiguous external genitalia, bifid scrotum, very small penis and tiny testes in the scrotal folds (Fraccaro, Kaijser & Lindsten 1960). On nuclear sexing the patient was chromatin positive and many of his oral mucosal cells showed three chromatin masses (Fraccaro & Lindsten 1960). The chromosome count gave a number of 49: his sex-chromosome constitution was XXXXY.

The frequency of chromatin-positive Klinefelter's syndrome has been estimated at approximately 1 in 500 males (Moore 1959, *Lancet* 1959). The condition is five to ten times more common among the intellectually subnormal (Prader *et al.* 1958, Ferguson-Smith 1958, Israelsohn & Taylor 1961). Among them it is found more often among the higher than the lower grades and is particularly seen among the non-differentiated types and among those with schizoid traits (Mosier *et al.* 1960). In a survey recently conducted by Dr G Jagiello (personal communication) at the Bexley Hospital in collaboration with the medical officers of the hospital, among 530 male schizophrenics, 5 were found who were chromatin positive, presumably XXY.

That there is an association between mongolism and Klinefelter's syndrome was first shown by Professor Penrose (Ford *et al.* 1959). More patients with this association have been reported. These patients have the clinical features of both conditions. They have 48 chromosomes, are trisomic for chromosome 21, and have an XXY sex-chromosome constitution. In four patients the maternal ages at the birth of the subjects are

known and were 43, 41, 38 and 20 respectively. The association between mongolism and Klinefelter's syndrome has also been noted in individuals belonging to the same sibship. Thus in 10 sibships selected for having a mentally defective patient with chromatin-positive Klinefelter's syndrome, 2 contained a mongol (Mosier *et al.* 1960). The frequency of an association between Klinefelter's syndrome and mongolism is unknown but on routine nuclear sexing of 49 male mongols at the Fountain Hospital, Dr G Jagiello (personal communication) found one with both syndromes.

The origin of the XO and XXY anomalies is attributed usually to non-disjunction during gametogenesis; normally the mature haploid gamete contains only 23 chromosomes, one of which is the sex chromosome. The sex chromosome may not be included (gametes with 22 chromosomes) or 2 may be found (gametes with 24 chromosomes). From the union with normal gametes of abnormal gametes without sex chromosome XO individuals arise with 45 chromosomes. Conversely, if the abnormal gamete possesses two sex chromosomes, its fusion with a normal gamete would result in the formation of XXY males with 47 chromosomes. Naturally if an abnormal XX gamete united with a normal X-containing gamete, an XXX individual would arise, the triplo-X female. Altogether about 10 triplo-X females have been described. In institutes for the intellectually handicapped their frequency is 0·7% (Fraser *et al.* 1960). They are chromatin positive with double masses; their chromosome number is 47 and on chromosome analysis, and with the aid of nuclear sexing findings, an XXX sex-chromosome complement is confidently established. Their clinical features are unremarkable apart from their intellectual subnormality and at least two of them have borne children and most have had normal menstrual periods. In the reported cases and among four who have not yet been reported there is a striking correlation between the condition and advanced maternal age at the birth of the affected individuals.

REFERENCES
Ferguson-Smith M A (1958) *Lancet* i, 928
Ferguson-Smith M A, Johnston A W & Handmaker S D (1960) *Lancet* ii, 184
Ford C E, Jones K W, Miller O J, Mittwoch U, Penrose L S, Ridler M & Shapiro A (1959) *Lancet* i, 709
Fraccaro M, Ikkos D, Lindsten J, Luft R & Kaijser K (1960) *Lancet* ii, 1144
Fraccaro M, Kaijser K & Lindsten J (1960) *Lancet* ii, 899
Fraccaro M & Lindsten J (1960) *Lancet* ii, 1303
Fraser J H, Campbell J, MacGillivray R C, Boyd E & Lennox B (1960) *Lancet* ii, 626
Israelsohn W J & Taylor A I (1961) *Brit. med. J.* i, 633
Lancet (1959) i, 237
Moore K L (1959) *Lancet* i, 217
Mosier H D, Scott L W & Cotter L H (1960) *Pediatrics, Springfield* 25, 291
Polani P E (1961) *Brit. med. Bull.* (in press)
Prader A, Schneider J, Francés J M & Züblin W (1958) *Lancet* i, 968

Dr Eliot Slater and Dr K Zilkha (*London*)

A Case of Turner Mosaic with Myopathy and Schizophrenia

This patient, a single girl aged 19 (Case No. 87810), was admitted to the National Hospital on 20.4.60. Her parents were first cousins; her three sibs are normal, but a maternal uncle's child had had a schizophrenic illness.

The patient, whose I.Q. is 92, did not do very well at school; and since then has never been fully employable, owing to her slowness. Menstrual history has been normal. Curvature of the spine was first noted at 13 but has not changed significantly since. Some weakness of the muscles appeared at the same age, and since then she has had difficulty in raising the head from a lying position.

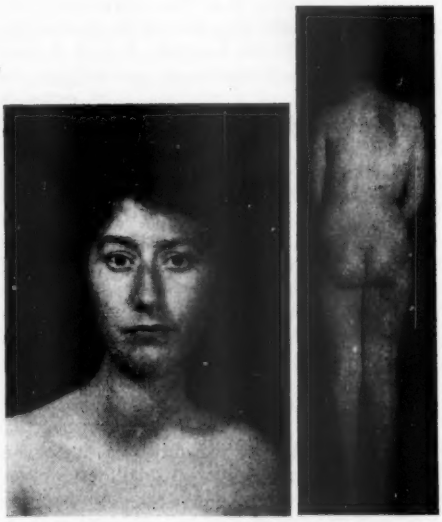

Fig 1 *View of face shows myopathic facies; on the right side of the neck there is an appearance resembling webbing, but this is probably within normal limits. Back view shows marked scoliosis*

The psychosis began in 1959, when she changed in attitude to her mother and would lock herself in her room and refuse to see anyone. In May 1959 she had her room redecorated but suddenly started stripping off the new wallpaper and wrecked the room. In July she burnt all her best clothes and went off to Brighton. Having arrived

there she found nowhere to stay, slept at the railway station and returned home next day. A few days later she cut off all her hair as close to the head as possible. On 13.8.59 she was admitted to Netherne Hospital where she was very agitated and disturbed. She was diagnosed as suffering from schizophrenia and treated with Stelazine and reserpine. Affect was recorded as incongruous; at times she was smiling to herself, at times near to tears. No delusions or hallucinations were noted; but there was thought disorder with difficulty in concentration and her talk was at times confused, with frequent interruptions. She eventually settled down, and was then transferred to the National Hospital for investigation of the weakness of the neck.

On admission, though quiet and slow, she showed no mental abnormality of a schizophrenic kind. On neurological examination there was bilateral facial weakness, severe weakness of both sternomastoids, weakness of the right scapular muscles, the right deltoid and both triceps muscles. Dr E A Carmichael thought the muscular weakness was due to old poliomyelitis; but this was thought unlikely by Dr R W Gilliatt, owing to the symmetrical weakness of the facial muscles and wasting of the sternomastoids. EMG studies of the right deltoid, pectoralis and rhomboid muscles on two occasions showed in all three muscles slight reduction in motor unit interference pattern on maximal voluntary effort; the motor units were brief, polyphasic, of reduced amplitude. The changes resembled those of a myopathy. A biopsy specimen from the right deltoid showed no abnormality. The EEG was normal. Otological examination showed moderate bilateral deafness, chiefly in the band 4,000–8,000 c/s. Vestibular function was normal, apart from some slight general reduction of caloric responses. Dr C S Hallpike reported that the cause was obscure. The Ishihara test was normal. Blood-films showed typical 'drumsticks' in 10/500; but buccal epithelial cells were chromatin negative. Professor Penrose reported that the blood culture cells might be those of a mosaic Turner's syndrome with about one-fifth of the cells lacking one X chromosome, while the others were probably normal: 'The skin culture cells did not seem to support this view, although there seemed to be quite a number of abnormal karyotypes. As this occurs in cultures not infrequently, I am inclined to discount them and to consider that she probably has the karyotype of a normal female.'

Fig 1 shows the myopathic facies and the scoliosis. The syndrome is interesting, combining unaccountable deafness, an unusual form of myopathy and a scoliosis not accounted for by muscular weakness. In view of the positive family history, the schizophrenic illness may be coincidental; as far as we knew this is the first case in which schizophrenia has been reported in a case of Turner's syndrome, pure or mosaic. The fact that the patient is the child of first cousins is curious. We wonder whether parental consanguinity can be expected to show in excess in such cases.

Meeting April 11 1961

Paper

Children of Psychotics – A Controlled Study [*Abridged*][1]

by Valerie Cowie MD DPM (*London*)

This investigation was designed to examine the hypothesis that one would not expect an increase of neurotic traits among the offspring of psychotics. This central hypothesis of the investigation was genetical and was based on the assumption that neuroticism and psychoticism are (as is generally accepted) separate and constitutionally unrelated. Certain environmental effects of psychosis in a parent have also been selected for consideration.

[1]This material represents part of an investigation which is to be published in full in *Acta Psychiatrica et Neurologica, Scandinavica*

Method

The offspring of a group of psychotic parents were compared with the offspring of a group of control parents with respect to indications of neuroticism. The psychotic (proband) parents were drawn from in-patients admitted to the Maudsley and Bethlem Royal Hospitals. Patients likely to fulfil the criteria for selection were first seen shortly after admission, and investigations of members of their families were carried out during the in-patient period. The diagnoses of the psychotic parents on discharge from hospital to fall into one of the following categories of the International List of Diseases and Causes of Death (Geneva 1947): (1) Schizophrenic Disorders (Diagnostic Code 300·0 to 300·7). (2) Manic Depressive Reaction (Diagnostic Code 301·0 to 301·2). (3) Involutional

Melancholia (Diagnostic Code 302). (4) Obsessive Compulsive Reaction (Diagnostic Code 313).

Patients in categories (2) and (3) were reclassified for the purpose of the investigation into those with affective illnesses of early onset, and those with affective illnesses of late onset, patients with late onset having shown the first signs of psychosis at 45 years of age or later, or having been diagnosed as suffering from involutional melancholia (Code 302). The inclusion of patients with obsessive compulsive reaction in a psychotic group may be open to question, but they were included because it is widely claimed that the incidence of neurosis is especially high amongst the children of obsessionals.

The control parents were selected from patients attending hospital for reasons other than that of psychotic illness. They were drawn from patients attending three general hospitals and one hospital for neurological disorders. They included inpatients with orthopædic and neurological disorders and patients attending physical medicine, diabetic and antenatal clinics. They were matched for age and sex with the psychotic parents.

The information about the offspring of the proband and control parents was obtained in interview with one of the parents in every case and sometimes with both. A full psychiatric history, with special attention to childhood development, was taken for each of the offspring. Supplementary data were obtained in some cases from the offspring themselves, and from hospitals, doctors, psychiatric social workers, local authorities and other agencies.

To convert information to numerical form, a neurotic symptomatology rating scale was introduced as follows:

0 = Good adjustment; absent or negligible neurotic symptoms.
1 = Sporadic signs of neurosis, e.g. isolated instances of sleepwalking, in an otherwise well-adjusted and non-neurotic individual.
2 = Persistent or chronic neurotic disturbance, but no treatment sought.
3 = Severe persistent neurotic disturbance, or neurotic disturbance for which treatment had been sought.

In addition to anamnestic data two questionnaires were used. These were the Teacher's Report Form (TRF) (Bowlby *et al.* 1956) and the Maudsley Personality Inventory (MPI) (Eysenck 1959).

Results

The distribution of the psychotic parents according to sex and diagnostic category is given in Table 1. Information was obtained for 330 of their offspring (age range 2 to 55 years; mean age 19·6 years) and for 342 offspring of controls (age range 2 to 55 years; mean age 19·7 years).

Table 1
Proband parents

Diagnostic category	*Male*	*Female*
Affective psychosis – early onset	12	29
Affective psychosis – late onset	18	28
Schizophrenia	12	33
Obsessive-compulsive reaction	6	14
Total	48	104

When results from the whole group of proband offspring were compared with those from the whole group of control offspring, the main findings supported the hypothesis that on a genetical basis an increased incidence of neuroticism would not be expected amongst the offspring of psychotics. Thus a slightly higher proportion of offspring of controls than of probands obtained a zero score, denoting absent or negligible neurotic symptoms. The MPI scores indicated that the level of neuroticism in the control offspring group was raised but that the level of neuroticism in the proband offspring group was not raised, the results being compared with those of Eysenck(1959) for a group of 1,800 English normals. Furthermore, no significant difference was found between the TRF adjustment scores of children of probands and of controls. The mean maladjustment scores were very slightly higher for proband children than for control children, though not significantly so.

Besides results for testing the main genetical hypothesis, findings of more general psychiatric interest were obtained in the course of the investigation.

When the proband groups were considered separately according to parental diagnostic category, there were strong indications that neurotic disturbance was more frequent amongst the offspring of obsessional probands than amongst the offspring of the other diagnostic groups. This was reflected in the numerical data obtained, and in the anamnestic data which revealed a tendency for the children of obsessionals to be overdependent on the mother and commonly subject to excessive faddiness with food, excitability, stubbornness, temper-tantrums, timidity, an inclination to cry

easily, attention-seeking behaviour, specific fears, and gratification habits such as cloth and thumb sucking. The number of offspring of obsessional probands studied was too small for these findings to be regarded as more than suggestive. The results suggest that further psychiatric study on a larger scale of the children of obsessionals would be of interest.

In the neurotic offspring of schizophrenic probands were features commonly associated with the schizoid temperament, such as undue sensitivity, irritability, over-excitability, solitariness, excessive day-dreaming and a tendency to retreat into a fantasy world. This was interesting in view of the genetical observations by Bleuler (1941) and Mayer-Gross *et al.* (1960) that persons of schizoid personality are frequently found amongst the close relatives of schizophrenics. On the other hand an environmental factor was evident as in the neurotic offspring of schizophrenic mothers, though not in those of schizophrenic fathers, the onset of neurotic symptoms was more frequently associated with very adverse circumstances in the environment than in the case of neurotic offspring in any other group.

The adverse environmental effect of a psychotic parent was supported by a comparison of the offspring of proband groups of parents with affective illness of early and late onset. If psychosis appearing in a parent were an environmental influence predisposing towards neurosis in the child, then this effect would be less likely to be observed in families in which the parent's psychosis first appeared at a later age, when the offspring are more likely to have less environmental contact with the parent or even to have grown up and left home, than in families of parents whose psychosis had started early. Support for this hypothesis was found in the higher percentage of zero scores on the neurotic symptomatology scale for the offspring of parents with affective psychosis of late than of early onset. Moreover, the mean neuroticism score on the MPI was lower for offspring of parents with affective psychosis of late than of early onset.

If the presence of a psychotic parent were an effective environmental factor in producing neurotic disturbance in the child, then it would be reasonable to expect a time relationship between the psychosis in the parent and the neurotic signs in the child. Furthermore, if such a relationship existed a higher incidence of neuroticism in the offspring would be expected after onset of parental psychosis than before, this effect being most marked in the period immediately after the onset of parental psychosis. A significant difference was found between the observed and expected distribution with respect to the time of onset of neurosis in the off-spring and the time of onset of parental psychosis, due mainly to an excessive incidence of neurosis in the offspring in the two-year period immediately after the onset of psychosis in the parent. Thus the view was supported that a causal relationship exists between the onset of parental psychosis and the appearance of neurotic manifestations in the offspring.

It has been suggested that children in the earliest years of life are especially vulnerable to certain kinds of psychological stress producing neurosis. Thus Bowlby (1940) has indicated that maternal deprivation is particularly harmful. This view has been strongly supported by other observers. The idea of special susceptibility to interruption in the mother-child relationship in the first two years of life is supported by the findings of Lewis (1954) in her work with deprived children. She found a significant difference with respect to disturbance between those children who were separated and those who were not, only where separation was lasting and occurred before the age of 2 years.

A test was made in the present investigation to ascertain whether the onset of parental psychosis at any particular age in early life would constitute such an environmental stress factor. In the children who were 15 years old or under, a distribution according to neurotic symptomatology rating and their age at the time of onset of psychosis in the parent showed no significant deviation of observed from expected values. The findings, therefore, failed to support the view that the onset of parental psychosis might constitute a stress conducive to neurosis to which the offspring might be particularly susceptible in the first two years or at any other particular age in early life according to the groupings studied.

Summary of Findings

In this investigation into the incidence of neurosis amongst 330 offspring of psychotic parents and 342 offspring of control parents, a comparison of the groups supported the hypothesis that on a genetical basis a raised incidence of neurosis would not be expected amongst the offspring of psychotics.

There was, on the other hand, evidence supporting the environmental hypothesis that psychosis in a parent is conducive to neurotic disturbance in a child. This included the finding of a lower rate of neurosis amongst the offspring of psychotic

parents with affective illnesses of late onset than amongst those of parents with affective illnesses of early onset when greater environmental contact might be expected between parent and child. Furthermore, an examination of the time of onset of psychosis in the parent relative to the time of onset of neurotic disturbance in the child indicated a causal relationship between these two events. The onset of parental psychosis did not, however, appear to be a stress factor to which the child was especially susceptible during the first two years of life if results could be measured in terms of neurotic symptomatology.

REFERENCES

Bleuler M (1941) Course of Illness, Personality and Family History in Schizophrenics. Leipzig

Bowlby J (1940) *Int. J. Psycho-Anal.* **21**, 1

Bowlby J, Ainsworth M, Boston M & Rosenbluth D (1956) *Brit. J. med. Psychol.* **39**, 211

Eysenck H J (1959) The Manual of the Maudsley Personality Inventory. London

Lewis H (1954) Deprived Children. London

Mayer-Gross W, Slater E & Roth M (1960) Clinical Psychiatry. London

Meeting November 8 1960

A discussion was held on **The Use of Psychiatric Skills in Industrial Organizations:** the opening speakers were Dr J J O'Dwyer and Dr Elliott Jaques.

Meeting December 13 1960

A meeting was held jointly with the Medico-Legal Society at which the subject under discussion was **Medical Evidence and its Presentation in Court.** The opening speakers were Dr Northage J de Ville Mather and Mr Henry Elam; Dr J A Hobson and Mr Phineas Quass QC opened the subsequent discussion.

The meeting has been fully reported in the *Medico-Legal Journal*, 1961, **19**, 71.

Section of Physical Medicine

President R W Windle MD

Meeting February 8 1961

Shoulder-hand Syndrome

by Malcolm Thompson MD MRCP
(*Newcastle upon Tyne*)

The interesting symptom-complex known as the 'shoulder-hand syndrome' is an unusual rheumatic disorder. This year, 1961, marks the centenary of the outbreak of the American Civil War, and from their observations on the wounded, Mitchell *et al.* (1864) first described the post-traumatic dystrophy which they termed causalgia – the name being a contraction of caustic algia, and descriptive of the intense, burning pain which their patients suffered. Since then a further ten painful dystrophies have been designated. When the descriptions of these conditions are studied they are found to possess a fundamental similarity irrespective of their site and method of presentation (Table 1).

Table 1
Dystrophic conditions of the upper limb

Causalgia (Mitchell *et al.* 1864)
État physiopathique (Vulpian 1875)
Sudecks' atrophy (Sudeck 1900)
Peripheral trophoneurosis (Zur Verth 1929)
Chronic post-traumatic œdema (Klassen 1929)
Post-traumatic painful osteoporosis (Leriche & Fontaine 1930)
Reflex dystrophy (de Takats & Miller 1943)
Post-infarctional sclerodactylia (Johnson 1943)
Reflex sympathetic dystrophy (Evans 1947)
Shoulder-hand syndrome (Steinbrocker 1947)
Reflex neurovascular dystrophy (Steinbrocker *et al.* 1948)

The shoulder-hand syndrome or 'reflex neurovascular dystrophy of the upper limb' is characterized by a painful stiff shoulder associated with, followed by, or preceded by a painful dystrophy of the ipsilateral hand and fingers. The wrist, elbow and other tissues of the arm are also involved, although the most striking changes occur in the shoulder and hand. The condition is often bilateral, the involvement of the contralateral arm being milder than the process on the side originally affected.

The clinical course of the condition has been conveniently divided into three stages. The first stage, of onset, may be rapid or insidious. Once established the process is usually progressive, and the first stage lasts three to six months. There is apparent pericapsulitis (periarthritis) of the shoulder and uniform, dusky-red, firm œdema of the hand and fingers of the corresponding side. The skin is hot, dry and tender to the lightest touch. Persistent burning pain is a distressing symptom, and movements are limited. X-rays reveal a diffuse osteoporosis with areas of patchy demineralization in the hands which may develop within a few days of the onset.

The second stage also lasts several months and the process, or part of it, may subside during this stage or may progress. Usually there is some diminution in the intensity of the pain, some improvement in shoulder movements and less hand œdema. Stiffness and flexion deformities of the hand may improve, remain static or progress. Atrophy of the subcutaneous tissues and muscles develops and early palmar fascial and joint contractures may ensue.

These changes inaugurate the third stage, in which the dystrophic changes are prominent. The skin is smooth, thin and inelastic with loss of the normal folds. The hand is cold and cyanosed and the nails are coarse and brittle. The small joints of the hands are stiffened and held in flexion while the shoulder is 'frozen' in adduction. There is general wasting of the upper limb musculature, and X-rays reveal diffuse, severe osteoporosis with intact bony margins at the joint lines.

The diagnosis is established on the clinical appearances, the frequent association with an identifiable pathogenetic factor, and the radiological changes. The principal differential diagnosis is from rheumatoid arthritis. The strict, upper limb localization of the shoulder-hand syndrome, diffuse œdema of the hand, normal

Some Uncommon Rheumatic Syndromes

E.S.R. (unless there is a coincidental or associated illness that elevates the E.S.R.) and a negative Rose-Waaler differential agglutination test, should suffice to separate the conditions.

The syndrome is known to be associated with a variety of medical and surgical conditions (Table 2) which occur so consistently in relation to shoulder-hand syndrome that it is reasonable to indict them as provocative factors. The inclusion of epilepsy as a provocative factor is made here for the first time.

Table 2
Provocative and associated factors in shoulder-hand syndrome

Myocardial infarction	Electro-convulsant therapy
Trauma	Pulmonary lesions
Cervical spinal lesions	Herpes zoster
Hemiplegia	Panniculitis
Brain tumour	'Vasculitis'
Epilepsy	

Several authors (de Takats & Miller 1943, Evans 1947, Steinbrocker *et al.* 1948) have separately postulated the reflex mechanisms which they considered responsible for the production of the syndrome. The process may be initiated by painful stimuli from the arm or thoracic structures, or from disturbances within the nervous system. The reflex activity thus established has an efferent circuit provided by the spinal autonomic and motor roots of the lowest four cervical and first thoracic segments. The principal stimuli and afferent arcs of the reflex are listed in Table 3. While many of the responsible afferent stimuli arise within the tissues later implicated in the resultant musculoskeletal changes, it is clear that many of the provocative factors emanate from segments far removed from C4 to 8 and T1.

Table 3
Anatomical classification of provocative lesions and their reflex paths

Provocative factor	*Afferent path*
Injury to hand or arm, Amputation stump pain } Post-traumatic causalgic state	Peripheral nerves
Cervical disc and bone lesions	Spinal nerve roots
Vasculitis in thoracic and axillary vessels	Periarterial sympathetic fibres
Visceral lesions, e.g. pulmonary tumours, myocardial infarction	Sympathetic afferents
Cord lesions, e.g. herpes zoster	Neuronal synapses
Cerebral lesions	Vasomotor centres in cortex and corticospinal tracts

Steinbrocker *et al.* (1948) have invoked the role of the 'internuncial pool', which is a diffuse network of interconnected neurons in the grey matter of the spinal cord, in order to explain the reflex pathways involved. Stimuli can reach the internuncial pool *via* sensory nerve roots, sympathetic afferents or from fibres in the corticospinal tracts. Disturbances in these neurons may spread radially to neurons in the lateral and anterior portions of the cord and exert their influence on the arm structures *via* the locomotor and autonomic efferent nerve roots. Spread through the internuncial pool may also account for the bilateral incidence of the shoulder-hand syndrome.

This hypothesis provides an explanation for the spread of the reflex through several cord segments; and the extent of radial diffusion could determine the severity and incidence of the vasomotor and musculoskeletal lesions. Some of the symptoms and signs of the syndrome may be attributed to stimulation of autonomic efferents and some to their destruction. Although not completely satisfactory this hypothesis is the one most compatible with the clinical data.

In a series of 17 patients suffering from shoulder-hand syndrome seen at the Royal Victoria Infirmary between January 1957 and December 1960, there were 9 men and 8 women. Only 3 patients were under 50 years of age. The provocative and associated clinical features in this series are listed in Table 4. The most striking differences between this series and others that have been reported (Evans 1947, Rosen & Graham 1957, Steinbrocker *et al.* 1948) are, first, the inclusion of epilepsy as a provocative factor; secondly, the high incidence of cerebral and neurological causes; and thirdly, the low proportion of idiopathic cases (1 only). Eight patients had bilateral signs, 6 had signs on the right side only and 3 on the left side.

Table 4
Associated features in 17 cases of shoulder-hand syndrome

Epilepsy	6
Meningo-encephalitis	1
Myocardial infarction	2
Cervical spondylosis	1
Herpes zoster	2
Drug coma and trauma	1
Hemiplegia	1
Epithelioma and cervical glands	1
Idiopathic	1
Ætiology uncertain (? coronary artery disease ? epilepsy)	1
	17

Of the patients suffering from epilepsy, none had neurological or focal electroencephalographic signs at the time of presentation with the shoulder-hand syndrome, and further neurological investigation failed to reveal any evidence of a space-occupying cerebral lesion, with one

exception. This patient was investigated for epilepsy dating from 1954, treated for acute bilateral shoulder-hand syndromes in August 1957, and developed signs of a left-sided hemiplegia in March 1960. Further investigations then confirmed the presence of a right parasagittal meningioma which was successfully excised. The shoulder-hand syndrome not only antedated the neurological signs but also responded to treatment in this patient although there was a persistent and progressive cerebral lesion present.

The only similar report in the literature is that by Thurel & Guillaume (1938) of a 63-year-old man who had twelve attacks of right-sided Jacksonian epilepsy in nine months, then developed a painful, swollen right hand with osteoporosis and, at the same time, a right facial paralysis. One month later he developed a right hemiplegia, and died four days after excision of a left-sided meningioma. It is postulated that cerebral lesions by anatomical or functional interference may disturb the control exercised by vasomotor centres located in the parietal cortex, the presumed area being Fulton's area 6. The resultant concentration of effect in the sympathetic chain and ganglia of the lower cervical and upper dorsal regions would account for the localization of the syndrome.

The remaining patients suffering from epilepsy and shoulder-hand syndrome are being followed with special regard to the development of neurological signs. It appears that cerebral lesions constitute an important ætiological factor in the genesis of the shoulder-hand syndrome. The influence of such lesions, in addition to the peripheral factors listed, must be borne in mind in all possible cases of shoulder-hand syndrome, including the *formes frustes* or painful stiff shoulders without significant hand involvement. The occurrence of dystrophic signs and symptoms in the upper limb may be an important neurological finding in cerebral disorders, indicating the site of the pathology in advance of conventional neurological symptoms and signs.

REFERENCES
de Takats G & Miller D S (1943) *Arch Surg.* **46**, 469
Evans J A (1947) *Ann. intern. Med.* **26**, 417
Johnson A C (1943) *Ann. intern. Med.* **19**, 433
Klassen P (1929) *Mschr. Unfallheilk.* **30**, 309
Leriche R & Fontaine R (1930) *Presse méd.* **38**, 617
Mitchell S W, Morehouse G R & Keen W W (1864) Gunshot Wounds and Other Injuries of Nerves. Philadelphia; p 164
Rosen P S & Graham W (1957) *Canad. med. J.* **77**, 86
Steinbrocker O (1947) *Amer. J. Med.* **3**, 402
Steinbrocker O, Spitzer N & Friedman H H (1948) *Ann. intern. Med.* **29**, 22
Sudeck P (1900) *Arch. klin. Chir.* **62**, 147
Thurel R & Guillaume J (1938) *Rev. Neurol.* **69**, 56
Vulpian E F (1875) Leçons sur l'Appareil Vaso-moteur Faites à la Faculté de Médecine de Paris. Paris
Zur Verth M (1929) *Mschr. Unfallheilk.* **30**, 309

Polymyalgia Rheumatica

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This paper describes 21 patients suffering from a syndrome which, as the result of a number of publications during the past ten years, is now becoming a well-recognized entity in rheumatic clinics. The name 'polymyalgia rheumatica' was first suggested for this syndrome by Barber (1957), and in the most recent paper, Gordon (1960) also adopts this name and gives a full review of previous literature.

The present series of cases has been seen at the Middlesex Hospital during the twelve-year period 1948–1960, and comprises 13 women and 8 men; at the time of onset of the disease the age range was from 46 to 76, with a mean of 61·2 years.

Symptoms

The clinical picture is remarkably uniform. The patient is usually a woman over the age of 50, who gradually develops increasing pain and stiffness affecting the muscles of the shoulders, neck and upper arms. The hips, thighs and low back are usually affected to a lesser extent, and there is no pain in the periphery of the limbs. The symptoms may take several months before reaching their peak, but less commonly the onset is more acute. The pain is aching, continuous, worse after movement or when tired, and to some extent improved by rest. Immediately after rest, however, it is usually worse again, and associated with marked stiffness.

Apart from the local symptoms, general disturbance of health has been present in all our cases. These general symptoms always appear early, and in some cases may precede the local symptoms by a month or two. Severe depression has been a feature of all our cases, and marked lassitude and some loss of weight have also frequently been present. A low-grade pyrexia has occasionally been noted in the early weeks of the condition.

Clinical Signs

Muscles: The most remarkable feature found on examination is the severe limitation of movement which affects principally the shoulder joints and hips, but may also affect the cervical and lumbar spine. Indeed, except for the age group and sex incidence, in severe cases the clinical picture closely mimics ankylosing spondylitis with shoulder and hip involvement. This extreme limitation of movement appears to be due to muscle spasm and tenderness, since all joints remain radiologically normal throughout the course of the disease, except for pre-existing

degenerative changes such as would be expected in this age group. In severe cases it is unusual for the patient to be able to abduct the arms to above shoulder level, and cervical movements may be limited to a few degrees in each direction; limitation of hip movement is not usually so severe, and generally flexion of the hips is more painful and limited than rotation, which is comparatively free.

Muscle tenderness is variable, but in our experience always present to some degree. In a few patients it appeared to be so severe that even light pressure caused considerable pain. The most constantly tender muscle appeared to be the deltoid, with biceps, trapezius, para-cervical muscles, and pectoralis major involved in this order of frequency. In the legs, the quadriceps group were most commonly involved, followed by the glutei, hamstrings, and deep muscles of the lumbar spine.

Wasting of the affected muscles does not occur, and true weakness is never a feature of this disease, apparent weakness being due to unwillingness on the part of the patient to contract the painful muscles strongly.

Joints: Transient swellings of peripheral joints occasionally occur, particularly of the knees, but symptoms are usually slight and short-lived, so that this feature of the condition may be overlooked if not carefully searched for. Other authors (Porsman 1951, Bagratuni 1953, Gordon 1960) have noted the occurrence of these transient joint swellings. One patient in our series (Case 6), although initially quite typical of polymyalgia rheumatica, later developed a peripheral arthropathy indistinguishable from rheumatoid arthritis.

Other clinical features: General examination revealed no abnormality unexpected in this age group (e.g. hypertension), except for a general exaggeration of deep tendon reflexes, which may well have been an expression of muscle tenderness and spasm.

Laboratory Investigations

Erythrocyte sedimentation rate (E.S.R.): As noted by other authors, a much raised E.S.R. is a constant feature of this syndrome. As in rheumatoid arthritis, the E.S.R. to some extent mirrors the clinical picture, gradually falling as improvement occurs, though in 2 cases the E.S.R. remained raised long after clinical recovery.

Anæmia: Moderate hypochromic anæmia is common, though not invariable, and tends to improve without therapy as disease activity subsides. As suggested by Gordon (1960), it may be associated with the free use which such patients make of aspirin in an attempt to relieve their pain.

Plasma proteins: Some increase in plasma globulin is common in severe cases, though this is never great, and is confined to the α_1 and α_2 fractions. We have not recorded any significant increase in the γ-globulin fraction.

Electromyography and muscle biopsy: Both these examinations have been carried out in 6 cases, and muscle biopsy alone in 1 case. In all cases the deltoid muscle was chosen for both investigations, as it appeared to be the most commonly and most severely affected muscle, and is easily accessible to investigation. Electromyography showed an entirely normal pattern in all 6 patients, and all the muscle biopsies were also normal. Although they were not specifically looked for, we have not seen the perivascular changes in muscle septa described by Gordon (1960).

Other investigations: Total and differential white cell counts have been universally normal.

Differential sheep-cell agglutination tests (SCAT) have also been negative in all cases except one (Case 8), and this patient has now fully recovered without developing any clinical evidence of rheumatoid arthritis.

Radiography of the whole spine and sacro-iliac joints, both shoulder and both hip joints, has shown degenerative changes consistent with age, but no other abnormality. In several of our patients barium enema revealed a long and redundant sigmoid colon, which is also an unusually common finding in rheumatoid arthritis.

A summary of the clinical picture and investigations is given in Table 1.

Treatment

Rest, physiotherapy, and salicylates appear to exert no effect upon the disease. Indeed, it has been our impression that physiotherapy in any form has produced aggravation of symptoms. Of 13 cases given phenylbutazone, or its analogue, Tanderil, however, 7 obtained dramatic relief of symptoms and 3 were significantly improved. This symptomatic improvement persisted in all 10 cases until the disease process abated, and enabled the patients to lead a normal life. In all cases reduction of the dose or withdrawal of the drug was followed by a prompt relapse of symptoms. The usual dose required was 100 mg thrice daily, and in view of this, we believe that phenylbutazone should always be given a trial before steroid therapy is considered. Six patients had symptoms severe enough to warrant a trial of steroids, and all of them made a good

Table 1
Summary of symptoms and investigations

Case No.	Sex	Age	Symptoms				Muscle tenderness	E.S.R.	Hb (g%)	SCAT	Proteins		
			Sh	Cs	Th	Ls					Alb.	Glob.	Electrophoresis
1	F	55	+	+	+	+	+++	48	12·3				
2	F	45	+	+	+	+	+	48	12·8				
3	F	54	+	+	+		0	36	10·0		4·6	3·1	α_2+
4	M	64	+	+	+	+	+++	58					
5	F	65	+	+	+	+	++	58	10·9	1 : 2	4·1	2·0	α_2+
6	F	69	+	+	+	+	0	71	7·0		3·4	3·1	α_2+
7	F	64	+	+	+	+	+++	65	8·6	1 : 8	3·6	3·1	α_1 & α_2+
8	F	69	+	+	+	+	++	43	12·6	1 : 64	3·7	2·7	N
9	F	68	+	+	+	+	+	54	11·6	1 : 16	4·1	3·8	α_1 & α_2+
10	M	62	+	+	+	+	+	17	13·8				
11	M	51	+	+	+		+	30	13·5	1 : 2	3·9	3·2	N
12	F	76	+		+		++	38	12·1	1 : 4	4·4	3·8	α_1 & α_2+
13	M	63	+	+	+		+	36	12·0		3·4	2·8	N
14	M	46	+	+	+	+	+	45	15·6	1 : 4	4·3	2·7	
15	F	65	+		+		+++	31	11·8		4·1	2·1	α_2+
16	F	56	+	+	+		++	46	12·6				
17	F	53	+		+		++	25	12·3	1 : 2			
18	M	66	+		+		++	20	12·6	1 : 8	3·7	2·7	N
19	F	67	+	+	+		+++	51	10·9	1 : 8	3·6	2·8	N
20	M	48	+	+	+	+	+++	39	13·8	4 : 3	2·7		N
21	M	75	+	+	+	+	++	52	12·8	1 : 4	3·4	2·6	N

Symptoms: Sh = shoulders Cs = cervical spine Th = thighs Ls = lumbar spine
Muscle tenderness: 0 = nil + = slight ++ = moderate +++ = severe N = normal
E.S.R. = Wintrobe (corrected) SCAT = sheep-cell agglutination test

Table 2
Response to treatment

Case No.	Treatment	Response to treatment	Follow-up (months)	Disease duration (months)	Remarks
1	Salicylates	+	78	18	Complete recovery. Raised E.S.R. persists
2	Salicylates	+	67	12	Complete recovery. Raised E.S.R. persists
3	B.T.Z. 100 mg t.d.s. Prednisone 5 mg b.d.	++ +++	53	53	Developed polyarteritis nodosa, controlled by prednisone
4	B.T.Z. 100 mg b.d.	+++	51	9	Complete recovery
5	B.T.Z. 100 mg t.d.s. Prednisone 5 mg b.d.	0 +++	36	36	Complete recovery
6	Salicylates	+	24	24	Now has rheumatoid arthritis
7	B.T.Z. 100 mg b.d.	++	48	24	Complete recovery
8	Salicylates	+	35	15	Complete recovery
9	Salicylates	0	30	15	Complete recovery
10	Salicylates	+	34	12	Complete recovery
11	B.T.Z. 100 mg t.d.s. Prednisone 5 mg b.d.	++	36	36	Side effects from B.T.Z. Symptoms relapse if prednisone withdrawn
12	B.T.Z. 100 mg b.d.	+++	18	12	Complete recovery
13	B.T.Z. 100 mg t.d.s. Prednisone 5 mg t.d.s.	+	24	12	Complete recovery
14	B.T.Z. 100 mg t.d.s.	+++	25	12	Complete recovery
15	Prednisone 10 mg b.d.	+++	60	60	Relapses if prednisone withdrawn
16	Tanderil 100 mg t.d.s.	+++	5		Still under treatment
17	Prednisone 5 mg t.d.s.	+++	13		Still under treatment
18	B.T.Z. 100 mg b.d.	+++	84	9	Complete recovery
19	B.T.Z. 100 mg b.d.	+++	18	12	Complete recovery
20	B.T.Z. 100 mg t.d.s.	+++	23	12	Complete recovery
21	B.T.Z. 100 mg t.d.s.	0	12	12	Complete recovery

Response to treatment 0 = Nil + = Slight benefit ++ = partial relief +++ = Complete relief
B.T.Z. = Phenylbutazone

response to prednisone in doses of 15 mg per day or less. Once again, however, there was a prompt relapse of symptoms if the drug was withdrawn.

We have gained the impression that neither phenylbutazone nor prednisone in any way influences the natural history of the condition, since patients so treated took as long to recover as those on salicylates alone. Both drugs, however, may give excellent symptomatic relief and are justified in severe cases.

Course and Prognosis

Polymyalgia rheumatica appears usually to be a benign and self-limiting condition, since the great majority of our patients – whether treated by salicylates, phenylbutazone or prednisone – have shown recovery to normal health in a period varying from one to three years (Table 2). Excluding those still with symptoms, mean disease duration was 14·8 months. Since recovery is a slow and gradual process, it is difficult to define with any accuracy when normal health has been regained, and the figures in Table 2 indicating disease duration can therefore only be regarded as approximate.

At follow-up, several patients admitted to slight aching of the shoulders or thighs after exercise, but not severe enough to limit activity or warrant the taking of analgesics.

Differential Diagnosis

Diffuse muscular pain and tenderness can herald the onset of several differing diseases, notably polymyositis associated with the collagen group of diseases or with malignant disease. In the former, other systemic symptoms and signs are nearly always apparent, and often (e.g. dermatomyositis) profound weakness is a dominant symptom; in the latter, wasting and weakness rather than pain and stiffness are the leading symptoms.

Paulley & Hughes (1960) have suggested that all cases of polymyalgia rheumatica are in reality examples of giant cell arteritis or arteritis of the aged. These authors consider that muscle pain and tenderness are merely a stage in the development of giant cell arteritis, in which the classical stigmata of that disease have yet to develop. Follow-up of our own patients does not support this view, as so far none has developed ocular or other systemic manifestations as might be expected if this hypothesis were correct, with the exception of Case 3, which is probably an example of polyarteritis nodosa. We would agree, however, that the early symptoms and signs of both conditions may be almost identical, and that the passage of time may be necessary before the two diseases can be differentiated.

Discussion

We believe that polymyalgia rheumatica is a distinct clinical syndrome with a remarkably constant pattern of symptoms and physical signs. It is more common in women than in men, and usually begins after the age of 50. Its course is usually benign and self-limiting, and uninfluenced by treatment, though both phenylbutazone and steroids give excellent symptomatic relief. We agree that the syndrome probably belongs to the collagen group, and that it is more closely allied to rheumatoid arthritis than any other condition.

We have not been able further to elucidate the ætiology, nor do we even believe that it can as yet be said for certain that the condition is primarily a disease of muscle. The symptoms and signs would appear to indicate fairly gross pathology within the affected muscles, yet both electromyography and muscle biopsy (admittedly in a small number of cases) have so far proved normal. A vascular basis for the condition seems unlikely in view of the limited anatomical distribution of affected tissue. If muscle spasm and tenderness are secondary phenomena, then affection of periarticular or bursal tissue would offer the most likely explanation of the syndrome.

The name 'polymyalgia rheumatica' is unwieldy and largely meaningless except in so far as it indicates the site of pain and suggests a collagen disease, but it is preferable to 'anarthric rheumatoid disease' (Bagratuni 1953) as there is no evidence that it is a variant of the rheumatoid syndrome. As we are no nearer to the elucidation of the ætiology, we consider it best to continue the name 'polymyalgia rheumatica' rather than confuse the picture by a new terminology.

REFERENCES

Bagratuni L (1953) *Ann. Rheum. Dis.* **12, 98**

Barber H S (1957) *Ann. Rheum. Dis.* **16, 230**

Gordon I (1960) *Quart. J. Med.* **29, 473**

Paulley J W & Hughes J P (1960) *Brit. Med. J.* ii, 1562

Porsman V A (1951) In: *Proc. II Congr. europ Reum.* **(Ligue Européenne contre le Rhumatisme.)** Barcelona; p 479

Speculations on Allergic and Infective Arthritis

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It is becoming increasingly fashionable to invoke various hypersensitivity and auto-immunity phenomena as ætiological factors in rheumatoid arthritis. By contrast, the clinical concepts of the relationship between allergy and arthritis are vague and unsatisfactory. Similarly, the term 'infective arthritis' is still used by clinicians without any clear idea as to the pathogenesis they are invoking. Furthermore, it is notable that clinical allergists and specialists in infectious diseases see little 'rheumatism' and almost no 'arthritis' in

their practices. In the few authenticated cases which do occur, the syndromes tend to be self-limiting and insignificant so that chronic polyarthritis is seldom a sequel. Such contrasting clinico-pathological concepts merit further discussion.

In his 1958 Heberden oration Ragan (1959) discussed the role of hypersensitivity in the pathogenesis of rheumatoid arthritis. He pointed out that the primary lesion of rheumatoid arthritis is a vasculitis whose pathology is mimicked almost exactly by that seen in the arthritis of serum sickness or experimental allergic arthropathy. Because these conditions are self-limiting, he postulated an additional auto-immunity factor to explain the self-perpetuating type of reaction which occurs in chronic polyarthritis.

If clinical allergy does bear a pathogenetic relationship to arthritis it must be a complex one, since certain allergic conditions such as asthma and hay fever have a definite antithetic relationship to rheumatoid arthritis. This was vividly illustrated by a woman of 43 who developed her acute and crippling rheumatoid disease on the same day that her asthma suddenly disappeared after having affected her daily for the past thirteen years. She suffered no further asthma attacks until her arthritis was brought under control, when the two conditions started to alternate in severity. Another feature of her disease, and alternating with the asthma and the arthritis, was severe migraine leading on one occasion to total amblyopia. Kersley (1954) drew attention to the same antithetic relationship in 6 patients he had observed.

In Table 1 are listed some conditions in which an associated immunological disorder has been invoked to explain the arthritis or arthralgia which sometimes occurs with them. There may be more than one type of hypersensitivity involved in these conditions. Furthermore, in the drug group, hypersensitivity may on occasion be confused with toxicity (e.g. hydrallazine).

While they last, however, allergic and infective arthritides bear a close clinical and pathological resemblance to rheumatoid arthritis and it is interesting to speculate not only on why they occur but why they do not persist.

To invoke a secondary auto-immunity factor in chronic arthritis as a result of an alteration in the connective tissue which renders it antigenic, merely creates the further problem of deciding what protective mechanisms exist in normal people, which presumably are deficient or absent in arthritics. Certainly traumatic, infective, allergic, and other insults to the connective tissue must occur universally, yet they very rarely give rise to self-perpetuating disorders. It would seem wiser therefore to regard them as 'trigger' factors in predisposed subjects rather than as the cause of chronic polyarthritis.

The 'focal sepsis' theory as an explanation of chronic polyarthritis is no longer in fashion. It is now agreed that the resulting vogue of speculative surgery on teeth, tonsils, appendices and gall-bladders was unjustifiable and occasionally disastrous. Such remissions as occurred were short-lived and were probably the result of the stress stimulus to the patient's own suprarenal cortices. Nowadays, surgery is only undertaken if

Table 1

Hypersensitivity infective and toxicity states in which arthralgia and/or arthritis may occur

Known allergen	*Bacterial sensitivity*	*Probable virus infection or sensitivity*	*Drugs*	*Allergen unknown or controversial*	*Allergic conditions antithetically related to arthritis*
Serum sickness Food allergy Spirit and wine allergy Gout (some cases)	Rheumatic fever Scarlet fever Erythema nodosum 'Gonococcal rheumatism' 'Tuberculous rheumatism' (Poncet's disease) 'Focal sepsis' in any part of the body	Influenza Hepatitis Infectious mononucleosis Mumps Measles Smallpox Poliomyelitis Rubella Herpes zoster Behçet's syndrome Bornholm disease Lymphogranuloma inguinale 'Royal Free disease' 'Hollander's syndrome' (Graham 1960)	Penicillin Hydrallazine Sulphonamides Thiouracil Iodides Bromides Neoarsphenamine Triamcinolone (Wells 1958)	Intermittent hydrarthrosis Palindromic rheumatism Purpura rheumatica Reiter's syndrome Polyarteritis nodosa Disseminated lupus erythematosus	Asthma Hay fever ? Migraine

the tissue concerned merits removal on its own account and not because of a suspected relationship with a rheumatic process. On the other hand, most authorities regard the polyarthritis of rheumatic fever as a hypersensitivity reaction resulting from infection with the Group A hæmolytic streptococcus.

Truelove (1960) emphasized the relationship between erythema nodosum and a syndrome which included morning stiffness, joint swelling, effusion, and tenderness. Indeed, these symptoms frequently preceded the skin manifestations by up to seven weeks. The E.S.R. was raised in over 50% of the cases, sometimes to very high levels. The condition was essentially benign although the joint symptoms persisted for many months in some cases.

Erythema nodosum is regarded as frequently being due to a hypersensitivity to tubercle bacilli, or streptococci. It is therefore an excellent example of a benign rheumatic disease apparently mediated through an immunological mechanism secondary to infection.

The exact nature of the antigen in such 'infective' syndromes is not known but it would seem that experiments to determine whether it was an exotoxin or some protein fraction of the bacterium itself might yield useful information and even provide a method of inducing arthritis experimentally in suitable volunteers.

True virus arthritides are rare but well recognized. It is, however, difficult to be sure whether they represent a direct infection of the joints by the virus or some form of hypersensitivity mechanism resulting from the primary infection. The fact that the arthritic symptoms generally occur after the acute infection is settling down does perhaps suggest the latter process. It is therefore interesting to note that in a disease such as lymphadenoid goitre in which an auto-immune process is generally acknowledged, the suggestion has been made that a virus infection such as mumps may be responsible for the initial 'leak' which institutes the auto-immune process (Eylan *et al.* 1957).

Two recent studies of virus arthritis are worthy of comment in this connexion. Johnson & Hall (1958) described 10 cases of polyarthritis arising in cases of rubella about one week after the rash appeared and usually lasting about one week. Nine of these patients developed a positive latex test.

The other study is by Hollander and his colleagues (Hollander *et al.* 1957, Graham 1960), who gave a preliminary report at the 1957 International Congress of Rheumatology of an epidemic virus infection in 14 patients (of which the senior author and his wife were two). In these, a polyarthritis 'indistinguishable from rheumatoid arthritis' developed between seven and fourteen days following the infection. Five of these 14 patients eventually developed a positive titre for the rheumatoid factor. Another group of 7 patients who already had rheumatoid arthritis caught the virus infection and all suffered a severe exacerbation of their disease. The details of this study, together with the results of the comprehensive virological investigations which were carried out, are now complete and are due to be published. Apparently, the disease was self-limiting in every case although in some the symptoms persisted for many months.

Conclusion: In this short and selective review many more questions have been posed than answered. These may be summarized as follows:
(1) If hypersensitivity is an important ætiological mechanism in rheumatoid arthritis, how does it differ from other syndromes in which acknowledged allergy and arthritis are associated?
(2) Why do such syndromes occur so infrequently and why are they always self-limiting and non-erosive in character?
(3) What is the significance of a positive latex test or sheep-cell agglutination test in these benign syndromes?
(4) Does true 'infective arthritis' exist or do the bacteria and viruses concerned merely act as antigens – directly or by altering the connective tissue of the host to render it auto-antigenic?
(5) Why do certain allergic conditions such as asthma appear to antagonize the development of arthritis?

Before these questions can be answered, it will be necessary to overcome the apparently insoluble problem of producing an arthritis analogous to rheumatoid arthritis in an experimental animal.

An excellent review of the attempts which have been made to do this in the past and the problems involved has recently been published by Gardner (1960). In another review by Glyn & Holborow (1960) of the immunological aspects of rheumatoid disease the point is made that little progress in identifying relevant antigens is likely to be made until more subtle isolation procedures are available. By present techniques it appears that the native state of the material being studied is inevitably altered while it is being isolated.

REFERENCES

Eylan E, Zmucky R & Sheba Ch (1957) *Lancet* i, 1062
Gardner D L (1960) *Ann. Rheum. Dis.* **19**, 297
Glyn L E & Holborow E J (1960) *Ann. Rheum. Dis.* **19**, 197
Graham W (1960) In: Arthritis and Allied Conditions. Ed. J L Hollander. London; p 568
Hollander J L, Brown E M, Jessar R A, Hummeler K & Henle W (1957) *IX Congr. int. Rhum.* (Toronto) to be published
Johnson RE & Hall A P (1958) *New Engl. J. Med.* **258**, 743
Kersley G D (1954) *Lancet* i, 934
Ragan C (1959) *Ann. Rheum. Dis.* **18**, 1
Truelove L H (1960) *Ann. Rheum. Dis.* **19**, 174
Wells R (1958) *Lancet* ii, 498

Some Rarer Rheumatic Diseases

by A St J Dixon MD MRCP (*London*)

Rheumatology can be defined as the study of rheumatoid arthritis and diseases which resemble it. Leaving out common diseases of joints, and also the many infective conditions which may invoke joints, there are over thirty well-characterized rare conditions which may reasonably be mistaken for adult or juvenile rheumatoid arthritis. The following are a selection.

Behçet's Disease

Behçet's disease was, according to Feigenbaum (1956), first described by Hippocrates. To Behçet's original triad of aphthous stomatitis, genital ulcers and recurrent uveitis (Behçet 1937), Behçet and others have since added fever, unresponsive to antibiotics and often to corticosteroids, erythema nodosum-like lesions on the leg, disseminated pustules on the skin, often developing in sites where the skin has been pricked; neuroretinitic lesions, scattered thrombophlebitis and an arthritis. The latter is usually confined to one or two major joints, and may be transient, leaving no residua, or persistent. Not all cases are fatal. A virus ætiology has been suggested but not proved. A striking feature of a recent case was the development of curious subungual lesions. These were painless and started as well-demarcated areas of bluish discoloration under the nails, with later separation. They appeared to be thromboses of the vascular beds beneath the nails.

Myelomatosis-Amyloid

Myelomatosis can cause 'rheumatism' in five ways: (1) By painful bone lesions; (2) by causing hyperuricæmia and gout; (3) rarely, by direct invasion of synovium by plasma cells; (4) by causing secondary agammaglobulinæmia and septic arthritis; (5) by the development of generalized amyloidosis with joint lesions. The last variety can be grouped with the so-called 'primary amyloid', because the latter always shows some evidence of myelomatosis, if one looks hard enough. The suggestion has been made that primary amyloid is the residue of a burnt-out or partly healed myelomatosis. A recent patient, referred for a large, woody tongue and tachycardia, showed amyloid infiltration of the muscles, heart, spleen, tongue and liver. His original presentation had been that of rheumatoid arthritis affecting the knees, shoulders and wrists, with apparently typical stiffness, limitation and swelling, and a symptomatic response to prednisolone. When seen he still had fluid in both knees, with swelling and stiffness of the wrists with typical 'carpal tunnel' symptoms and median nerve compression. The mucous membranes of the lower lip were studded with grains of amyloid and his swollen tongue was printed with the impression of his teeth. There were also deposits in the conjunctivæ. Bence-Jones proteinuria had been present and an increase of plasma cells in the bone marrow. At autopsy the knee synovium was pale pink where it still retained dye some three months after a positive Congo red test had been obtained.

The wrists of another recent patient with myeloma-amyloid also showed typical carpal tunnel infiltration. Decompression operations relieved the median nerve paræsthesiæ. In addition to her typical myelomatosis, she had extensive amyloid of mucous membrane, conjunctivæ and skin, both around the eyes and also around the anus. Gafni & Sohar (1960) described excellent results in detecting amyloidosis by rectal biopsy. It seems to be a far more practical, painless and efficient way of getting the diagnosis than gum biopsy. In yet another patient (Dixon 1960), the resemblance to rheumatoid arthritis was even more marked, with joint pains and swellings, effusions and contractures of knees, and even elbow nodules (presumably myelomatous deposits). In that case, as in all the others I have seen, a negative Rose-Waaler differential agglutination test was a strong pointer towards the correct diagnosis and away from rheumatoid arthritis.

Hæmophilia

Webb & Dixon (1960) recently reviewed a series of patients with hæmophilia, in which X-rays of patients' joints were taken whether or not there had ever been joint pain. Twenty-four of these patients also had their anti-hæmophilic globulin (AHG) levels estimated. It was the severe hæmophiliacs who developed joint disease – those with less than 2% of AHG in their blood. The knees elbows, ankles and hips were most often involved, sometimes without symptoms. In reviewing this series four points were outstanding: (1) Enlargement of the radial head occurred and was often clinically visible; it was a common X-ray sign and had been present in the first X-ray ever to be published on this subject by Shaw in 1897. (2) In some patients, once a joint had been involved it was more, not less, liable to further hæmorrhages. (3) Since a hæmarthrosis seemed to predispose a joint to further bleeding, Webb & Dixon believed that one should treat the patient with an acute hæmarthrosis as a medical emergency and, under cover of a fresh plasma drip, or AHG if available, aspirate the joint and relieve the tension as soon as possible, not just splint and wait, as used to be recommended. (4) Bone lesions were found in some patients who could remember no local joint trouble. One patient showed marked cystic changes in the

carpus, yet the joint was normal. Another had painless limitation of one hip from cystic changes in the femoral head. It is not difficult to imagine episodes of bleeding into bone ends, rather than the joint itself, which, if extensive, could probably cause articular destruction by infarction of the joint surface, just as do nitrogen bubbles in caisson disease. Blood in a normal joint causes little harm and is not very painful, but once the bone end has been breached further hæmorrhages into the joint will be much more painful and destructive by seeping under pressure beneath the cartilage and into the bone itself.

Reticulohistiocytosis

The review by Warin and his associates at Bristol in 1957, is still the best, although scattered case reports have appeared since. The disease is characterized by the deposition of nodules without central necrosis, containing histiocytes with a hydrolysis-resistant proteolipid in their cytoplasm. Warin and his colleagues stressed the skin lesions as well as resemblance to rheumatoid arthritis. In a recent case, proved by biopsy, the patient had only three tiny papular lesions in the skin, but she had enormous numbers of lesions in tendons, and in tendon insertions and in bone ends. Her disease was clinically indistinguishable from rheumatoid arthritis at onset, in fact she was found in a follow-up study (Dixon 1960) of patients with rheumatoid arthritis who had shown a negative differential agglutination test. The nodules in the bone ends produced 'cystic erosions' resembling rheumatoid arthritis on X-ray. However, the bones were not porotic and the joint space, where not invaded, remained wide.

The knees showed similar but larger cystic appearances on X-ray and clinically showed effusions and slight contractures. It is possible that this disease may occur without skin lesions at all, in which case nothing short of biopsy would give the game away.

Jaccoud's Arthritis

Jaccoud published and illustrated in 1869 a report on the hand of a patient who had had repeated severe rheumatic fever and heart disease. The hand was remarkable for severe ulnar deviation without active arthritis. Many cases have been reported since, summarized by Bywaters (1950), who appears to have been the sole author on this subject in the last twenty years, with the exception of a paper from Manchester, which has in part been subsequently retracted. The concept is of a subluxing arthropathy due to softening and relaxation of ligaments without continuing inflammatory disease. Such changes in the bones and joints as are seen are secondary to the altered mechanics of the joint. These cases undoubtedly occur and the clinical picture is striking. In one patient the first carpometacarpal joint underwent a spontaneous painless passive dislocation in use. Biopsies have been done in a number of patients and show no active inflammation, but there is slight fibrosis and capsular scarring, with apparently healed 'erosions' which may be due to altered tendon or ligament pressure. Although the clinical picture is typical, none of the histological findings is specific and it is conceivable, though unlikely, that this is a mild, painless, burnt-out rheumatoid which, but for the associated heart disease, would not have come under medical scrutiny.

Examples of relapsing polychondritis, 'calcium gout', 'oxalate gout' and multiple joint lesions of osteomalacia and of hyperparathyroidism were briefly cited.

[The paper was illustrated by 31 slides and a list of 31 rare causes of non-infective polyarticular disease was circulated.]

REFERENCES

Behçet H (1937) *Derm. Wschr.* **105**, 1152

Bywaters E G L (1950) *Brit. Heart J.* **12**, 101

Dixon A St J (1960) *Ann. Rheum. Dis.* **19**, 143

Feigenbaum A (1956) *Brit. J. Ophthal.* **40**, 355

Gafni J & Sohar E (1960) *Amer. J. med. Sci.* **240**, 332

Jaccoud F S (1869) Leçons de Clinique Médicale faites à l'Hôpital de la Charité. 2nd. ed. Paris

Shaw J E (1897) *Bristol med.-chir. J.* **15**, 240

Warin R P, Evans C D, Hewitt M, Taylor A L, Price C H G & Middlemiss J H (1957) *Brit. med. J.* i, 1387

Webb J B & Dixon A St J (1960) *Ann. Rheum. Dis.* **19**, 143

Clinical Section

President T C Hunt DM

Meeting March 10 1961

Cases

Idiopathic Enteromegaly, Presenting with Two Unusual Surgical Complications

Paul T Savage MB FRCS

A E, male, aged 21

14.2.58: Admitted to the Whittington Hospital as an emergency, complaining of severe upper abdominal cramp-like pain and retching for three hours.

Previous health: Several similar attacks of upper abdominal pain, not so severe, during the previous three years.

On examination: An ill-looking man with considerable epigastric distension and splaying of lower ribs. Upper abdomen tympanitic. Gastric aspiration produced only a few millilitres of straw-coloured fluid. Supine and erect radiographs of abdomen showed a large gas-filled hollow viscus under the left dome of the diaphragm which was thought to be a volvulus of the stomach.

At operation (two hours after admission): He was found to have a *volvulus of the splenic flexure of the colon* through 180 degrees in two planes, with enormous distension of the twisted loop which was 23 cm in diameter (Fig 1). The volvulus was reduced and the distended splenic flexure decompressed through a hole in the transverse colon, into which a Witzel transverse colostomy tube was introduced.

Convalescence was at first uneventful; his bowels acted normally on the third day. On the fourteenth day the Witzel colostomy tube was removed. He developed a recurrence of upper abdominal distension over the next three days,

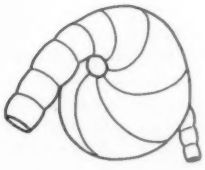

Fig 1 *Volvulus of splenic flexure of colon through 180 degrees in two planes*

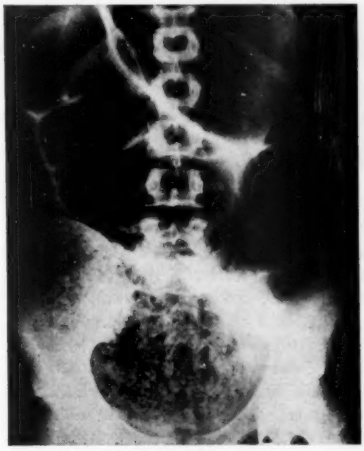

Fig 2 *Recurrent volvulus of splenic flexure of colon. Supine radiograph of lower abdomen showing grossly distended transverse colon*

Fig 3 *Recurrent volvulus of splenic flexure of colon. Supineradiograph of upper abdomen showing enormous distension of splenic flexure of colon*

Fig 4 *Recurrent volvulus of splenic flexure of colon. Erect radiograph of abdomen showing fluid levels in distended colon*

Fig 5 *Volvulus of splenic flexure of colon. Resected specimen*

Fig 6 *Strangulation obstruction of stomach through an aperture formed behind by the transverse colon, in front by the anterior abdominal wall, to which the transverse colon was united by omental bands*

due to a recurrence of the volvulus of the splenic flexure (Figs 2, 3, 4). The abdomen was therefore reopened and after reduction of the volvulus and decompression of the transverse colon, the left half of the transverse colon, the splenic flexure and descending colon were resected (Fig 5). Continuity of the bowel was restored by end-to-end anastomosis. The operation was completed by making a loop transverse colostomy near the hepatic flexure of the colon.

Histological examination of the resected specimen showed normal ganglia in the myenteric plexus both in the distended splenic flexure and in the narrrow descending colon resected with it.

Barium studies of the colon carried out during convalescence showed no evidence of Hirschsprung's disease. The colostomy was therefore closed.

During the next two years he was readmitted to hospital on three separate occasions with attacks of subacute intestinal obstruction. On two occasions the obstruction responded to treatment with 'drip and suction', but on the third occasion it did not.

At laparotomy (through the old mid-line scar) the cause of the obstruction was found to be an adhesion uniting a loop of ileum to the anterior abdominal wall scar, with kinking. The small bowel proximal to the obstruction was seen to be grossly distended and the ileum distal to the obstruction, although collapsed, was of very large calibre. At this operation the stomach was noted to be very large. The obstructing band was divided and the small bowel decompressed. Convalescence was uneventful.

1.7.59: He had an attack of pain in the right loin, strongly suggestive of renal colic. An I.V.P. showed a normally functioning left kidney and non-functioning right kidney. Right retrograde pyelogram showed a right hydronephrosis due to a pelvi-ureteric stricture.

2.11.60: He was again admitted as an emergency with severe upper abdominal pain, vomiting and upper abdominal distension. Supine and erect radiographs suggested a further attack of small bowel obstruction. A trial of conservative treatment with 'drip and suction' produced only a temporary improvement. At operation he was found to have a *strangulation obstruction of the stomach* through an aperture formed behind by the transverse colon, and in front by the anterior abdominal wall, to which the transverse colon was united by omental bands (Fig 6). The strangulated stomach was enormous and contained over 1,700 ml of fluid. Its wall was partly gangrenous and it ruptured as an attempt was made to dislocate it out of the abdomen. After emptying the stomach, a 2/3 Billroth I partial gastrectomy was carried out. The resected specimen was 40 cm in length around the greater curve and its mucosa showed severe hæmorrhagic infarction.

A barium meal carried out four weeks later showed the large size of the remaining gastric pouch.

There have been no further complications.

Intralobar Sequestration of the Lung

K P Abel MChir FRCS (for L L Bromley MChir FRCS)

This case is an example of a rare condition whose pathological criteria were only fully established by Pryce in 1946. These criteria are the existence of a systemic blood vessel, whose microscopic structure is that of a typical pulmonary artery as shown by the elastic wall, supplying a portion of the lung and arising directly from the aorta, the venous drainage being into the pulmonary vein; and, lastly, ectasia of the bronchi in the affected segment which do not communicate with the main bronchial tree.

Case History

An 8-year-old boy first presented in July 1959 with abdominal pain for the previous few hours due to pneumonitis of the right lower lobe in which an X-ray showed a cavity with a fluid level (Fig 1). This illness responded to postural drainage and antibiotic therapy. After the acute attack a bronchogram (Fig 2) was performed which failed to demonstrate any communication between the posterior segment of the right lower lobe and the rest of the bronchial tree.

The boy was symptom free until he developed a febrile illness three weeks before his admission on 19.2.61. Three days before admission he began to produce purulent sputum.

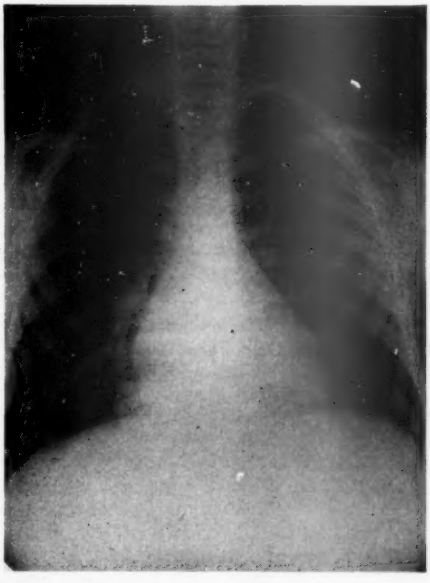

Fig 1 *A.P. view of chest July 1959*

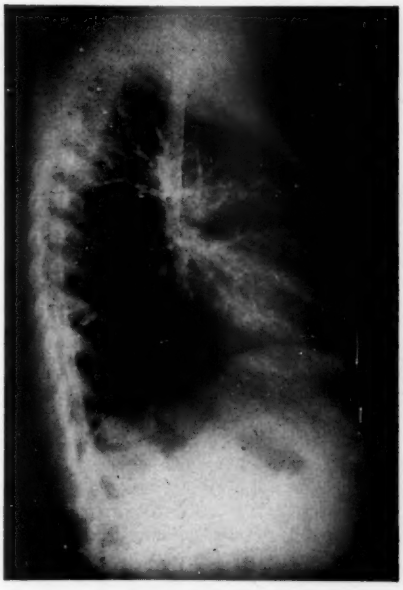

Fig 2 *Bronchogram September 1959 showing no fluid level*

An X-ray showed a recurrence of the fluid-containing cyst in the posterior segment of the right lower lobe. He was thought to have a congenital lung cyst and thoracotomy was performed by Mr L L Bromley, on 3.3.61, when the true nature of the condition became apparent. An aberrant systemic vessel (Fig 3) arising from the aorta, approximately the size of a femoral artery in a child of this age, was found in the inferior pulmonary ligament. There was a clear-cut line of demarcation between the normal lung tissue and the sequestrated portion. Right lower lobectomy

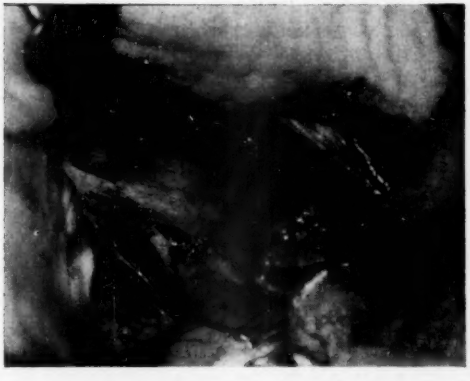

Fig 3 *Showing the dissected accessory artery*

was performed and the patient made an uneventful recovery. Pathological examination revealed ectasia of the lung, venous drainage to the pulmonary vessels and a pulmonary artery arising from the aorta (Fig 4).

Fig 4 *High power view stained with Weigert's elastic stain showing ectasia of the lung and typical pulmonary artery*

Discussion

When Pryce wrote his article only 3 cases of intralobar sequestration had been described and since then 120 have been reported. The importance of the condition for the thoracic surgeon lies in the great size of the aberrant pulmonary artery which can be a source of severe, even fatal hæmorrhage (Harris & Lewis 1940). Since intralobar sequestration may present at any age from the first to the seventh decade, it may have to be distinguished from lung cyst, tuberculosis or even carcinoma. The reason why many of these cases present with a lung abscess in which there is a fluid level, although the sequestrated segment does not communicate with the main bronchus, is that connexion develops as a result of inflammation in the sequestrated area.

The distinction between intralobar and extralobar sequestration has some practical significance. In extralobar sequestration both arterial supply and venous drainage are systemic; it may occur almost anywhere in the lung and in 90% of cases is associated with other congenital abnormalities most often with defects of the diaphragm on the left side, and in some cases with cysts of the mediastinum or upper abdomen. As pointed out by Abbey Smith (1956) the embryological reasons for extra- and intra-lobar sequestration probably differ. The clinical criteria for the diagnosis of intralobar sequestration are the characteristic position, a history of inflammatory episodes and failure to demonstrate communication between the main bronchial tree and the sequestrated segment.

REFERENCES
Harris H A & Lewis I (1940) *J. thorac. Surg.* 9, 666
Pryce D M (1946) *J. Path. Bact.* 58, 457
Smith R A (1956) *Thorax* 11, 10

The following cases were also shown:

Tetany Due to Duodenal Arterio-mesenteric and Ligament of Treitz Occlusions
Dr A R F Williams (for Dr S B Karani)

Multiple Jejunal Diverticulosis
Mr J W Bradbeer (for Mr N C Tanner)

Primary Pre-tibial Myxœdema with Hypothyroidism
Dr Ann Stokes (for Dr S B Karani)

Chronic Intussusception Due to Mucocele of Appendix
Captain R S Taylor (for Lieutenant-Colonel S H Janikoun)

A Female Case of Hæmophilia
Dr L Gilchrist
(An account of this case will be given in a later issue of the *Proceedings*)

Two Cases of Dupuytren's Contracture of Right Hand, Treated by Open Palm Technique
Mr C R McCash

(*Meeting to be continued*)

Section of Dermatology

President Hugh Gordon MC FRCP

Meeting January 19 1961

Cases

Epidermolysis Bullosa Dystrophica with Severe Deformity of Hands and Pharyngeal Stenosis, Relieved by Cortisone
E J Moynahan FRCP

C H, male, aged 14
This boy was referred with a view to gastrostomy because of the severe difficulty in swallowing he had experienced during the previous year as a result of repeated blistering in his pharynx due to the severe dystrophic epidermolysis bullosa from which he had suffered from birth.

History: Blisters were noted on the skin at birth, originally diagnosed as pemphigus, but blistering continued and the correct diagnosis was not arrived at until he was 2 or 3 months old, when his parents were given a hopeless prognosis. Since then blisters have occurred all over the body – including the inside of the mouth, throat, nose, and conjunctivæ. Only blisters on the skin surface had shown a tendency to improve. Most affected have been the feet, knees, elbows, hands, wrists, axillæ, buttocks, and back of the thighs; the blistering inside the mouth and pharynx had got much worse during the past year, and eventually he was incapable of swallowing any minced food which contained the smallest amount of fibre. The boy owes his life to his mother, who during infancy fed him through a fountain-pen filler, and during the past year has carefully ground up his food to enable him to swallow it. Even so, he is grossly stunted, and when he arrived at Great Ormond Street his weight was less than 3 st. Very marked deformity of his hands began to set in between the age of 4 and 5, when the thin, atrophic skin began to form a continuous sheath, covering the clenched fingers of both hands.

It was decided to try to improve his general condition before attempting gastrostomy, and in view of previous success in suppressing blisters in severe epidermolysis bullosa, he was put on cortisone, 300 mg daily, on September 13 1960 for a week. The dose was gradually reduced during the next two months, since when he has been on a maintenance dose of 25 mg daily. During this time his body weight increased 50%, from just under 3 st to 4 st 7 lb. During the same period he grew $\frac{3}{4}$ in. in height. One of the results of steroid therapy was to decrease the obstruction in his pharynx, so that the lumen, which had previously been as narrow as 1·5 mm, increased in six weeks to over 7 mm. Blistering was virtually completely controlled on this dose, and it was decided to attempt reconstruction of his hands. This has been successfully accomplished by Mr David Matthews, on the right side, and it is hoped to tackle the left hand later in the year.

On admission the skin was blister free. He presented with considerable wasting and dwarfing. The mouth was almost completely denuded of epithelium. Swallowing was painful and difficult – almost impossible. The teeth showed some caries. The upper canines protruded. The bite was considerably restricted and the lower jaw underdeveloped. The skin on the knees, hands, feet and elbows was extremely thin and atrophic, and the deformity mentioned above was present in both hands.

Progress: Dramatic improvement with steroid therapy, appetite increased, and he was able to swallow more easily within a few days of starting treatment. He gained weight rapidly, but as he had a small stomach capacity, he tended to feel over-full after quite a small meal. His condition eventually improved so satisfactorily that there is now no need to consider gastrostomy, and plastic reconstruction of his hands was given first priority.

Comment: The published reports on the treatment of epidermolysis bullosa with steroids are not very encouraging but their value in controlling the blistering in the severest forms of the disease was made evident to me nearly two years ago when I tried them in a really desperate case of the

lethal variety of this rare congenital and heritable malady. Although we lost the baby boy we had the satisfaction of suppressing the blistering completely for a time. This experience led me to revise my views on the role of steroids in the treatment of this disorder and since then I have used them routinely in all cases of the dystrophic forms of the disease, and have been successful in controlling the blistering in every case since then. In all patients which show blisters at birth it is important to begin treatment as soon as possible because delay in starting treatment leads to much higher doses being required to control blistering. The maintenance dose is quite small and the patient should be left with a few blisters so that overdosage is avoided. That cortisone and allied compounds are effective should be quite clear from this case where we have not only controlled the blistering but have made it possible for plastic reconstruction of his severely deformed hand to be successfully carried out, and I would like to thank Mr Matthews for his great interest and very skilful management of the difficult surgical problem which this boy presented.

Professor J T Ingram: I have seen this boy once previously and I congratulate Dr Moynahan on the result he has achieved. He was very undernourished and I thought in terms of gastrostomy. I believe that this condition of the hands is due to bandaging. I am interested in the response to steroids, especially of the œsophagus. These problems are rather tragic. I believe that this boy is very intelligent and co-operative. I do not known whether that is common with epidermolysis bullosa, but it is most marked with this patient and is a great help.

Dr C H Whittle: We have seen and shown a boy, now aged 9, with very similar skin changes: this child is also very intelligent and co-operative. He has an excellent mother and I believe he owes his life to her. I am impressed by the effect of the heroic doses that have been mentioned. We thought at the time of trial that steroids were useless for our patient, but we may well have given far too small a dose.

Dr B C Tate: I agree with Dr Whittle. One question is the right dose and how soon one should start giving it. Should we start from birth, as soon as the case is diagnosed, or should we wait to see how a case goes on?

The President: Perhaps with this condition one simply has to make an assessment in each case.

Dr E J Moynahan: From my experience with the series I have treated at the Hospital for Sick Children I would answer emphatically that treatment with steroids cannot be started too soon as the earlier the blistering develops the more severe the condition is likely to be and the more urgent is the need for treatment. The condition behaves rather like a forest fire which can usually be extinguished in its early stages when few trees are alight, but which can destroy the whole forest despite all efforts once it gets a firm hold: the analogy holds for steroids in those diseases which they suppress. The dosage in every case is a matter of trial and error; the aim should be to suppress the blistering and then gradually reduce the dose to acceptable maintenance levels. Of course the dose in some severe cases may be very high and the physician will run into trouble. It is a risk which must be taken if patients are not to die in default of treatment or because treatment was not adequate. The 'lethal' variety is going to be fatal unless something is done and steroids offer us the only hope at present.

Dr J Overton: In 1952 I looked after a 7-week-old boy exhibiting severe manifestations of this disorder. Two brothers were said to have died in the first month of life of the same condition. I put the child on 50 mg cortisone a day with oral Aureomycin initially. Partial control of the lesions was achieved and then oral Aureomycin was replaced by Aureomycin ointment locally. The child died on the forty-seventh day of his cortisone treatment from a fulminating pneumococcal meningitis and early pneumonia, proved *post mortem*. The onset of the complications, detected only twenty-four hours before death, was insidious and silent, suggesting that this is one of the dangers of relatively high systemic corticosteroid therapy, particularly when given at this age.

Dr D E Sharvill: The question of intelligence is interesting, because these children do get very backward educationally. I recall a boy in his teens who had been diagnosed as suffering from psoriasis, but he had epidermolysis bullosa. He was sent to King's College Hospital, and had bullæ right down the œsophagus. It was before cortisone came to be used and he was not treated with it. He is of above average intelligence, but he has missed many years of schooling.

Dr G A Beck: It is perhaps rather difficult to decide so young. I saw one such case that was being transfused at birth and the pædiatrician had great difficulty because everywhere he touched it the skin fell to pieces. He managed to complete the transfusion and keep the child alive for a week or two. She gradually recovered without any steroids at all and is now 2 years of age. She shows a few scars where the blisters were during the first few hours. But during the first fortnight of that child's life I think one would have been very tempted to put her on steroids. I should like to know whether one can tell as early as that which cases are going to do well and which are going to need steroids.

Dr E J Moynahan: Blistering in the mouth may persist until late in life and carcinoma may supervene in the atrophic and scarred mucosæ as it may, of course, in atrophic skin elsewhere in this disorder; epitheliomata developing in badly scarred areas, such as the hands in this boy, have necessitated amputation in a number of patients. I agree that there is a tendency for all forms of epidermolysis bullosa to improve as the patient grows older but I would doubt the diagnosis in any case which exhibited cutaneous disintegration of the severity seen in Dr Beck's case. An alternative dia-

gnosis is Ritter's disease in which Nikolsky's sign is often positive and would account for the skin separating wherever the infant was touched; drug rashes due to bromides and iodides may be congenital and exfoliate.

Nævoid Hypertrophy of the Lower Limbs, with Gigantism of Digits (Klippel-Weber-Trénaunay Syndrome)

E J Moynahan FRCP

K C, female, aged 13 months

History: The condition was noticed at birth, when extensive port-wine staining was seen to involve both lower legs and buttocks. The left great toe and the 2nd and 3rd digits of the right foot were larger than their fellows on the opposite side. The left foot shows an unusual cleft running from the first interdigital space in a semilunar direction across the sole similar to that seen in some Mongols. Since she was first seen in June 1960 there has been considerable paling and breaking-up of the port-wine stain.

Pregnancy was normal. She has one sib (sister aged 4½ years) who is well. There is no family history of skin disorder or any other abnormality.

The child is beginning to walk and has passed the usual milestones for her age.

Investigations: X-ray shows no deformities of the hip, but gigantism of the phalanges in the affected toes is obvious.

Comment: Hæmangiectatic hypertrophy of a limb, usually lower, although uncommon is not as rare as one might imagine. I see a number of cases showing this developmental anomaly each year at the Hospital for Sick Children. Girls are affected more often than boys and the left side seems to be involved more frequently than the right suggesting some mechanical factor in development, analogous with that seen in the pathogenesis of microphthalmia in the chick, where compression of main vessels on one side of the head during development may be responsible. The condition may involve half of the body and give rise to true hemi-hypertrophy: bilateral and contralateral involvement occurs. Gigantism of the whole limb may be produced or the hypertrophy may be confined to part of the extremity, as in the present case, where there is gigantism of the toes.

This anomaly and allied congenital angiomatous conditions leading to increase in size of the affected part are obviously due to developmental anomalies in the whole or part of the vasculature of the region affected. It has been described under various designations by different authors, depending upon which vascular element predominates: for example, congenital phlebectasia (Bockenheimer 1907); angiectasis (Smith 1882) or congenital varicose veins (Petit 1880). In this country, cases of hypertrophy of the lower limb associated with hæmangiomata were shown by Hawthorne (1902) and Roxburgh (1902). Parkes Weber (1907) saw a case in which nearly all of the left side was involved but Little had previously reported a similar case involving the right side in 1893. Klippel and Trénaunay's classic paper did not appear until 1900, but the condition had long previously been recognized by Virchow (1855) and Hebra & Kaposi (1876) as elephantiasis telangiectodes and Rokitansky had given a good account of the pathology. The German authors recognized the congenital origin of the malady but regarded it as a new growth and mistook the significance of the connective tissue although they noted that the vascular elements usually predominated.

Many of the milder cases tend to improve as the vascular channels close down with increasing age of the child; more severe cases in which arteriovenous communications are numerous or well established may develop gangrene in the affected limb or cardiac failure associated with the left ventricular hypertrophy which is a consequence of the altered circulatory hydrodynamics so that amputation may be necessary.

REFERENCES

Bockenheimer P (1907) Festschr. f. G.E. v. Rindfleisch. Leipzig, p. 311
Hawthorne C O (1902) *Rep. Soc. Stud. Dis. Child., Lond.* **2**, 114
Hebra M & Kaposi M (1876) Diseases of the Skin, Vol. 3. Sydenham Soc., London; Vol. 61
Klippel M & Trénaunay P (1900) *Arch. gén. Méd.* N.S. **77**, 641
Little J F (1893) *Trans. clin. Soc. Lond.* **26**, 243
Petit L H (1880) *Un. méd. Paris* ser. III **29**, 316
Rokitansky C Von (1842) Handbuch der pathologischen Anatomie. Wien; **2**, 207
Roxburgh A B (1902) *Rep. Soc. Stud. Dis. Child., Lond.* **2**, 222
Smith T (1882) *Trans. clin. Soc. Lond.* **15**, 261
Virchow R L K (1855) Handbuch der speciellen Pathologie und Therapie. Wien; **1**, 317
Weber F P (1907) *Brit. J. Derm.* **19**, 231

Dr J R Simpson: I have seen two children with something like this and showed one here in November 1957. Nobody then suggested this rather delightful name for it, and I labelled it as the arborizing telangiectatic nævus of Parkes Weber. Am I right in believing it is the same condition? Both my patients had considerable difference in the length and girth of their lower limbs.

Dr E J Moynahan: That is quite right. The names given to this condition are rather confusing. Klippel is a German name, but he was French; Weber is British; Trénaunay sounds Cornish, but he too was French. I think that Dr Simpson's patients had this condition and not arborizing telangiectatic nævus.

Dr E Lipman Cohen: I have one small child under my care in whom I made this diagnosis. I should like to

know how seriously one must take the idea that this condition might lead to heart failure and what are the indications for obtaining the opinion of a surgeon for such a child.

Dr M Feiwel: Did Dr Moynahan imply that the limb had to be sacrificed in the majority of cases? If he did I do not agree with him.

Dr E J Moynahan: The milder cases get better without amputation, but if there is gigantism of any degree a majority of these will have to lose the limb. In most of these nævoid conditions, with temporary overgrowth in the early stages, the nævus seems to disappear as the child gets older and there is no need for interference.

Acquired Albinism with Intraocular Depigmentation

Anne Maguire MRCP (for E J Moynahan FRCP)

L K, male, aged 52, a postman, attended Guy's Hospital with blisters of the hands on 19.4.60. He had had rheumatic fever as a child. There was no relevant family or personal history.

On examination: Infected pompholyx of both hands. The patient's skin was completely depigmented, the entire body skin being pale except for a patch on the anterior surface of the neck, periorbital areas, and a small patch on the posterior surface of the neck; these areas were brown in colour. The scalp hair was white with a spattering of black hairs over the occipital area. The body hair entirely depigmented except for a few pigmented hairs on the anterior surface of the shins.

He stated that this condition began about thirty years ago while he was in the Army; at that time his Army pass book had stated his eyes were brown. One or two pale areas had developed on the extensor surface of both forearms. These gradually increased in size until the whole of the upper arms became depigmented. At this time he was abroad with the Army and suffered severe sunburn of these areas. During the course of the next few years the skin became depigmented on the lower limbs and trunk.

Six years ago he became aware that his eyes had turned from brown to blue.

During the past two or three years he had had great difficulty with his vision, particularly on bright sunny days, or when he glanced at a white surface, such as a white wall with reflected sunlight. He stated that his eyes hurt and that headaches developed.

Investigations: Minimal erythema dose (M.E.D.) was 15 sec at 18 in. (normal for this lamp is 40 sec at 18 in.). X-ray skull – normal pituitary fossa. X-ray chest normal. 17-ketosteroids 8·8 mg/24 hours. W.R. and Kahn negative. Liver function tests, E.S.R. and full blood count all normal.

Eyes (Dr P Gardiner): 'The condition is not seriously affecting the eyes, although he is photophobic. According to the patient's statement there has been loss of iris pigment (brown eyes becoming blue). However, a considerable amount of pigment remains and although the retinæ are well pigmented there is a pigment disturbance in the periphery of the left retina, particularly below and temporally.'

Incidentally, this patient had a basal cell carcinoma of the frontal area of the scalp.

Treatment: Pompholyx of the hands, treated with local applications of unguentum hydrocortisone 1%, cleared in two to three days.

Ophthalmologists are of the opinion that the photophobia will gradually become worse, and they wish to observe this patient during the course of the next few years. At first we thought we would label this case universal vitiligo, but now perhaps acquired albinism would be a more appropriate description.

Comment (Dr E J Moynahan): We brought this case because of the loss of pigmentation by the normally pigmented intraocular structures in association with the almost total vitiligo, and as we could find no record of vitiligo affecting the eye, although the eye is always involved in albinism and albinoidism (partial albinism). Albinism is generally believed to be due to the absence of the enzyme tyrosinase which is essential for the conversion of tyrosine into melanin (a defective enzyme would produce the same effect). This enzyme is present only in melanocytes and is controlled by various factors. A possible clue to the sparing of the ocular structures in most cases of vitiligo is to be found in the different embryonic origin of the melanocytes inside the eye from those of the rest of the body. The latter, as is well known, arise from the neural crest but those of the eye arise from tissue which separates before the formation of the neural crest. There is also a physiological difference in melanogenesis which seems to be limited to a very short period in development of the eye, in contrast with the almost continuous process in the skin and the equally permanent inhibition of its production by melanocytes at other sites.

Dr J Pegum: This is a most noteworthy case and it would be interesting to know what the skin looks like under the electron microscope. At the meeting of this Section held at the Royal Marsden Hospital in June 1960 we were shown some beautiful electron microscope photographs which illustrated that there is one sort of melanocyte in vitiligo and another in albinism. It raises the question of whether some of the condi-

tions we call vitiligo are not acquired albinism, if this is not too much of a contradiction in terms.

Dr E J Moynahan: I am thankful for this suggestion and as we now possess an electron microscope at Guy's we will certainly look into the matter. If there is an enzyme defect we should be able to investigate it by biochemical means: one should be able to distinguish between vitiligo and albinism. It has been suggested that vitiligo may be due to the secretion of a neurohormone by the sensory nerve endings which inhibit the secretion of melanin by the melanocytes. One should of course always bear in mind that certain individuals tend to lose pigment from their irides in later life – a change analogous with greying of the hair. That this is not so here is clear because of the depigmentation of the retina. It would seem, too, that the pigment is lost from the anterior part of the iris and is retained, at least to begin with, in the posterior part, where it is normally found in blue-eyed persons. This loss of pigment from the ocular structures certainly makes one think of the possibility of acquired albinism. It would be interesting to know what is happening to the melanin in the meninges round the brain-stem which is believed to correlate much more closely with the degree of skin pigmentation than does eye colour.

The following cases were also shown:

Ichthyosiform Erythrodermia of Brocq with Ocular and Nasopharyngeal Involvement
Dr M E Eiloart and Dr E J Moynahan

***Strongyloides stercoralis* Infestation with Cutaneous Manifestations (Larva Migrans)**
Dr K C Lee (for Dr E J Moynahan)

Case for Diagnosis ? Lupus Erythematosus
Dr E S Emslie (for Dr D I Williams)

Sarcoidosis in a Jamaican
Dr E S Emslie (for Dr R H Marten)

Annular Sarcoid
Dr R H Marten

Case for Diagnosis ? Monilial Granuloma
Dr P Borrie

Subcorneal Pustular Dermatosis with Unusual Histological Features
Dr B Woods (for Dr A Rook)

Meeting March 16 1961

Cases

Eccrine Poroma of the Sole
P J Hare MD MRCP

G B, male, aged 53, business man.

History: The lesion has been present on the right heel for about two years. It is painless and has not bled. It was not preceded by any recollected injury.

Clinical findings: On the plantar surface of the right heel there is a fleshy pink fungiform mass about one centimetre in diameter (Fig 1). It arises from a shallow depression in the sole and is surrounded by a slightly hyperkeratotic collar.

Biopsy: Histological examination of a small fragment shows hyperplastic epidermis overlying a somewhat vascular stroma. The epithelial component is composed of masses of small cells with prickles (Fig 2). There is no palisade at the periphery. In places, duct-like structures can be found. No PAS-positive, diastase-resistant material is present in the main cells of the tumour.

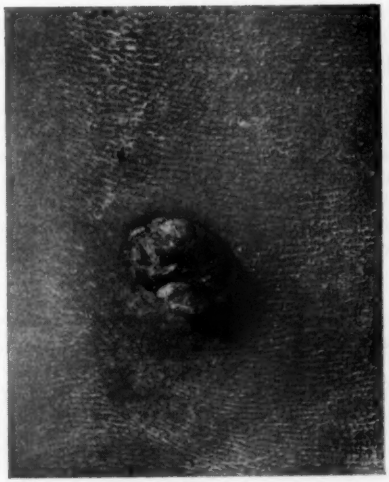

Fig 1

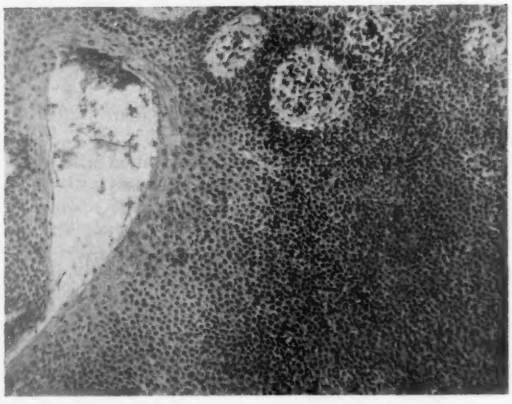

Fig 2

Comment: This case resembles those reported by Pinkus *et al.* (1956) as eccrine poromas, i.e. tumours derived from the intra-epidermal portion of the sweat duct. Knox & Spiller (1958) drew attention to the 'shallow, cup-shaped, epidermal invagination from which the tumours protruded' although in my experience this appearance is not peculiar to such lesions on the sole. In this country, analogous cases have been reported by Hunter & Hellier (1960).

REFERENCES
Hunter G A & Hellier F F (1960) *Brit. J. Derm.* **72**, 283
Knox, J M & Spiller W F (1958) *Arch. Derm., Chicago* **77**, 726
Pinkus H, Rogin J R & Goldman P (1956) *Arch. Derm., Chicago*, **74**, 511

Dr H Haber: This is a typical case, clinically and histologically.

A Film illustrating **Studies in Nail Growth** was shown by Dr P D Samman.

The film was a time-lapse study showing the changes in a nail over a period of five and a half months made possible by the co-operation of a medical student who attended twice a day every day. At the start of the film the nail was heavily infected with fungus, and became normal during treatment with griseofulvin.

Cases of **Photodermatitis Due to Tetrachlorsalicylanilide** were shown by Dr D S Wilkinson, Dr G C Wells & Dr R R M Harman, and Professor C D Calnan. These cases will be fully reported in a later issue of the *Proceedings*.

The following cases were also shown:

Parakeratosis Variegata
Dr M A Vickers (for Dr H R Vickers)

Pyoderma Vegetans
Dr B Woods (for Dr J A Leahy and Dr C H Whittle)

Subcorneal Pustular Dermatosis (Sneddon-Wilkinson)
Dr B Woods and Dr C H Whittle

? Cutaneous Leishmaniasis
Dr S Gold

Case for Diagnosis ? Sporotrichosis
Dr J Marks (for Dr S Gold)

Onchocerciasis
Dr G A Caron (for Professor C D Calnan)

Dermatofibrosarcoma Protuberans
Professor C D Calnan

Morphœa-like Basal Cell Epithelioma
Dr P D Samman

Case for Diagnosis – Rosacea with Tuberculoid Histology
Dr C J Stevenson

Subcorneal Pustular Dermatitis
Dr D S Wilkinson
(Meeting to be continued)

Section of Epidemiology and Preventive Medicine

President J A Fraser Roberts MD

Meeting February 17 1961

Paper

A Study of Control Methods in Tuberculosis

by James Grant MD DPH, E L Feinmann MB MRCP and K M Martischnig MD (*Gateshead*)

Dr James Grant

On the Tyne directly opposite Newcastle stands Gateshead, both towns together forming the greater part of the Tyneside conurbation. The population of Gateshead, never less than 100,000 in the present century, has consisted mainly of skilled, partly skilled and unskilled workers, who made up 91% of the working population in 1951, in comparison with the national percentage of 81·7. Most of these workers were engaged in the heavy industries and the related coal mining and processing, but in later years there has been an increasing diversion of labour to the varied light industries in the new local industrial estates.

A small village in the nineteenth century, the town in its rapid extension epitomized the horrors of Victorian industrialization. It suffered three epidemics of cholera in 1831, 1849 and 1853, the last of which was explored by the great Sir John Simon in the commission of enquiry. In 1884, the Local Government Board made a further enquiry into the continuous high mortality from the infectious diseases. Both reports reflect the evils of the nineteenth century in insanitary housing, lack of proper sanitation and of proper drainage and sewerage with an attendant overcrowding. Until fairly recently these factors continued to prejudice the health of the town for, in 1936, the official overcrowding survey placed Gateshead as the second most overcrowded borough in England, although a decline of population set in after the First World War.

Industrial depression brought Gateshead into the category of a distressed area, but with the threat of the Second World War the heavy iron and steel industries and coal mining revived, while the Team Valley Trading Estate was set up by the Government within the town, which began the march back to prosperity. Now great changes are taking place. Rehousing of the people from the slums goes on accompanied by the clearance and redevelopment of large areas. Thanks to the assistance of the Special Areas Commission, Gateshead achieved some notable hospital and clinic developments and was indeed very well supplied with hospitals in 1948.

Tuberculosis in Gateshead

Like other areas on Tyneside, Gateshead has all along been severely afflicted by the scourge of tuberculosis. Table 1 illustrates the variation of population in the last sixty years and the dreadful story of tuberculosis until ten years ago. In 1937 and 1938 Gateshead stood with South Shields and Middlesbrough as the worst county boroughs in England and Wales for mortality from tuberculosis and held the same position in the years 1948 and 1949. In these years the tuberculosis mortality was over 1 per 1,000 of population.

Table 1

Tuberculosis rates of Gateshead in the censal years (1901–1951) and in 1960

	Population	Deaths P.	Deaths N.P	Death rates per 1,000 P.	Death rates per 1,000 N.P.	Notifications P.	Notifications N.P.	Case rates per 1,000
1901	109,898	204	86	1·85	0·78	—	—	—
1911	116,928	146	60	1·24	0·51	—	—	—
1921	125,148	138	70	1·08	0·55	357	157	4·10
1931	122,379	143	39	1·15	0·31	259	132	3·16
1941	106,820	128	26	1·19	0·24	208	51	2·4
1951	114,700	47	11	0·41	0·09	237	34	2·32
1960	108,560	6	—	0·06	—	116	15	1·20

P. = Pulmonary
N.P. = Non-pulmonary

Anti-tuberculosis work started after the First World War but remained fairly primitive for many years, although a small tuberculosis hospital of 50 beds was opened in 1924 and provided with X-ray apparatus for the use of the one Tuberculosis Officer of the Local Authority, who worked also at a small Tuberculosis Dispensary. Notified cases of tuberculosis were often found to be in an

advanced stage of the disease when examined. In order to achieve earlier diagnosis, systematic examination of contacts was begun in 1933 and it was also arranged that practitioners would refer their patients directly to the X-ray unit in the chest hospital on one morning a week. These measures, in turn, led to earlier and better ascertainment of the disease and improved follow-up measures. Gateshead had many arrangements with other bodies for the reception and treatment of tuberculous patients, but in 1936 Gateshead joined a partnership with the other Durham county boroughs, South Shields, Sunderland, West Hartlepool and Darlington, and with Middlesbrough, in the erection of the Poole Sanatorium.

Table 2

Cases of pulmonary tuberculosis attending Gateshead Chest Clinic 1936–1960 and pulmonary deaths in Gateshead

		Infectivity		*Pulmonary*
	Cases	*T.B.−*	*T.B.+*	*deaths*
1936	186	80	106	104
1937	163	68	95	118
1938	172	72	100	115
1939	178	77	101	119
1940	157	65	92	129
1941	168	93	75	128
1942	196	89	107	107
1943	201	90	111	106
1944	231	125	106	122
1945	202	103	99	98
1946	219	111	108	75
1947	226	119	107	93
1948	226	128	98	99
1949	248	157	91	91
1950	222	139	83	64
1951	226	152	74	47
1952	243	159	84	45
1953	267	155	112	29
1954	201	115	86	38
1955	166	105	61	23
1956	242	148	94	18
1957	125	66	59	19
1958	121	62	59	23
1959	124	66	58	19
1960	116	74	42	6

The great improvement in the tuberculosis situation in Gateshead is shown in Table 2. A comparison of the tuberculosis death-rates of Gateshead with the national experience is worthy of note, for in 1960 for the first time the Gateshead rate was lower than the national. Although there had been a slow and uneven decline in tuberculosis mortality, it was not until about 1950 that a sharp fall began and this is attributed to the introduction of streptomycin and P.A.S. Latterly, the decline of mortality and incidence has been accelerated by the wider ascertainment of cases of the disease, still more effective therapy with the introduction of isoniazid and the effort to immunize contacts and school leaver children with BCG vaccine. Another measure of progress in the control of tuberculosis is to be found in the tremendous reduction, amounting almost to a disappearance, of miliary tuberculosis of the meninges and lungs from the community, which on the average accounted for 14 deaths per annum in the immediate post-war years.

In 1956, with the co-operation of the Regional Hospital Board, an attempt was made to carry out an X-ray survey of the population. During a period of roughly six weeks, three mobile units and two fixed units were mobilized to deal with the public, industrial workers and the older school population. Altogether 35,121 persons, or 44% of the population over fourteen years were surveyed, this number consisting of 18,359 members of the general public, 12,548 industrial workers and 4,214 school children over 14 years. As a result, 76 active cases of pulmonary tuberculosis were found, and 29 of these had a positive sputum, while the examination of the contacts of the patients yielded 2 more active cases. This accounts for the apparent increase of incidence in 1956 (Table 2).

Origin of the Present Study

In the autumn of 1956, Dr W C Cockburn of the Public Health Laboratory Service and Dr D Thomson of the Ministry of Health suggested that we should explore and compare locally the different approaches to the problem of extirpating tuberculosis. Broadly, the task was to intensify our efforts, using the means and methods already available rather than by mobilizing a special team, in a more extensive search for contacts of ascertained cases. For this purpose an additional special nurse was employed in September 1957, the necessary finance being found by the Medical Research Council. In March 1958 an Odelca 100 mm camera was established where it was easily accessible in the former tuberculosis dispensary in the grounds of the Health Department. This was a very considerable expansion of the miniature X-ray facilities already available at some distance in the Newcastle General Hospital with its attached mobile unit that was used for the examination of special groups such as factory workers on the Trading Estate. It was hoped that general practitioners would have every patient with a chest disability X-rayed.

The local authority staff had for some years been testing school entrants with tuberculin as a measure of infection in the community and testing older children for suitability for BCG vaccination. As an additional measure it was thought worth while to test some infants in the first year of life and follow them through to school life. With the finding of positive reactors it was hoped to investigate infected families. In the course of this work an issue arose as to the most convenient and rewarding method of performing the large number of tuberculin tests involved. Tuberculin

reactors among the school children were encouraged to submit themselves to miniature radiography of the chest and expectant mothers were similarly referred for routine chest radiography. Lastly, members of the general public who presented themselves at the Odelca Unit were welcomed.

For long it was known that great numbers of chronic infectious tuberculous patients were at large in the community. Attention was specially directed to these with a view to the repeated examination of their contacts and also to the prevention of the obvious dangers presented by these patients, of whom no less than 224 were counted in 1951, 146 being fully ambulatory and even working at that time, while living in their homes in contact with a total of 469 persons. It was obvious that the more chronic infectious patients were among the older age groups, particularly of males. The co-operation of the general practitioners in the town was sought in an effort to get all their patients aged 50 years and over examined by X-ray. Personal contact was made at a conference in the local chest hospital and the chest physicians and the Medical Officer of Health also attended the meetings of the local medical committee to encourage practitioners to co-operate with the plan. Practitioners were also reminded by circular letters to send all their patients over the age of 50 for chest X-ray examination, whether the illness suggested lung disease or not. It was made possible for practitioners to send specimens of sputum for special culture examination for tubercle bacilli as an alternative to the attendance of patients at the X-ray unit.

Regular conferences were held at which the results were assessed. These were attended by the Medical Officer of Health and members of his staff specially interested in childhood tuberculosis, the three chest physicians, the nurse specially employed for case finding and by Dr Cockburn.

Tuberculin Testing of Children

Using tuberculin jelly, the testing of tuberculin sensitivity in all school entrants was begun in 1951 and continued until 1955, when other techniques were used. At first over 20% of the children were found to react to this test, many of these positive reactions resulting from the consumption of raw milk. The area was scheduled for the compulsory pasteurization of milk under the appropriate legislation in 1953. In 1955, using the Heaf multiple puncture apparatus and the Mantoux intradermal techniques, only 6% of all school entrants examined were found to be tuberculin positive. In 1957, annual tuberculin testing of children born in 1956 was instituted and continued as far as possible until 1960, after which they would enter school. For this purpose Rosenthal's prong applicators were used to apply undiluted Old Tuberculin by means of a stainless steel plate or disc with four projections, which were pressed with the aid of a magnet firmly on the stretched skin of the arm. Although it was thought that the results should be comparable with those of the Heaf technique, certain comparative studies were made which led us to abandon the prong technique. It was felt that results might depend on the firmness of the pressure applied through the discs to the skin. Moreover, it proved to be inconvenient to sterilize the apparatus by ordinary methods.

In a number of tuberculous hospital patients the prong test was compared against the Heaf test, using the same tuberculin, and against a Mantoux 1/1,000 intradermal test. It was found that the Heaf gun and the Mantoux test gave strictly comparable results, but the prong test was unreliable on 25% of these. Compared with Mantoux tests at 1/100 and 1/1,000 dilutions of tuberculin it was found that the Heaf test was not quite so reliable as the 1/100 solution but slightly more sensitive than the 1/1,000. The Heaf method was found, nevertheless, to be the most convenient method for testing large numbers of children.

(*a*) *Children born in 1956:* These children were the subject of special testing repeated annually, as far as possible, in the years 1957–1960. 999 children were included in the original group, but this number declined in succeeding years, so that only 1,886 tests were actually carried out. 117 of these children had been given BCG vaccine as tuberculosis contacts, and excepting these, only 12 positive reactors were found, i.e. 1% of the original group. Search among the contacts of the naturally sensitive children led to the discovery of two adults who had infectious tuberculosis and of two symptomless primary lesions in the siblings of the survey children. Three of the positively reacting children lived within a narrow area wherein an attempt was made to test as many children as possible and to encourage the adults to attend the special X-ray unit. As a result, 148 children were tested, 2 were found to have active primary lesions, but 267 associated adults examined by X-ray were found free from infection.

(*b*) *School entrants:* In the years 1955–1960, 7,415 (77%) of the school entrants were tested by Mantoux or Heaf methods: 277 (3·7%) were found to be naturally positive reactors and 165 were found to have been the previous recipients of BCG vaccine. Whereas in 1955, 89 (6%) of 1,483 children were natural tuberculin reactors, in 1960 out of 1,185 entrant children tested only 24 (2%) were found to have been naturally infected, while 52 had previously had BCG vaccine. The 277 in-

fected children were examined at the Chest Clinic, but only 28 had evidence of possibly primary active infection, 52 others showed healed or calcified lesions and 199 had normal chest X-rays.

Efforts made to trace the sources of infection in these tuberculin-positive entrant school children met with little success, but in 1959 a very special effort was made by inviting the parents to come to the Chest Clinic for examination with the child. Out of 2,172 children tested, i.e. 80% of the entrants, 98 reacted to tuberculin, but 58 had previously had BCG vaccine. Of the 40 children who had acquired a natural sensitivity, 17 had already attended the chest clinic as contacts, 7 others were found to have active primary lesions and 16 children had neither an obvious lesion nor a history of contact with a possible source of infection. The mother of one child reactor was found to have active tuberculosis.

(*c*) *School Leavers:* After a pilot survey carried out in 1954, an attempt was made in the following years to select 13-year-old children suitable for BCG vaccine. In 1955, 293 (28%) of the 1,038 children reacted positively, but in 1960, 313 (22%) of 1,427 showed evidence of previous infection.

Altogether, 6,101 children when tested yielded 1,610 positive reactors (26%). Of these, 1,322 were submitted to X-ray examination, and as a result 6 children were found to be suffering from active pulmonary tuberculosis. It was not found practicable to trace the source of infection in such a large number of reactors.

Ascertainment of Cases

In the groups from which new cases of tuberculosis came to light, the patients specially referred with chest symptoms to the Odelca Miniature X-ray Unit by their own practitioners provided the biggest yield for new cases, while other successes were found by X-raying the groups of contacts of known cases. Yet these facilities were not used to the fullest extent either by suspects or contacts, although there were regular evening sessions each week. It seemed that, despite the efforts of the team and the local practitioners, many persons were unco-operative and this statement applies with some force to the men over 50 years of age. A comparison of the ages of the persons attending the special unit was of similar distribution to the age groups of the census of 1951. As it seemed to be of great importance to secure the diagnosis of tuberculosis where it existed, often in a chronic infectious form, special arrangements were made to culture specimens of sputum sent from such patients who were unwilling to attend for miniature X-ray examination. This approach, too, was a complete failure. On the other hand, very large numbers of the adult population were examined by the special X-ray unit and it did appear that, when discovered, the disease was generally detected at an earlier stage than had formerly been the case. This statement is based on a comparison of the percentage of patients in Category III attending the unit, with the experience in a year previous to its use.

At the beginning it appeared that the chronic infectious case of tuberculosis would be a major aspect of the problem but, as time went on, the importance of this factor regressed because of the death of the patients or the success of prolonged chemotherapy in bringing about non-activity. At the end of the survey the remaining chronic infectious cases were few in number or were in such circumstances, either living alone or with elderly contacts only, and not out working, that they no longer presented any great danger to the community. The distribution of tuberculosis by the spot map yielded no information, as it appeared that the disease was uniformly spread among the population as a whole. In the course of the study, it was noted that a patient with an apparently negative tuberculous infection considered to be healed could suffer a breakdown and become ill again. This change particularly was a menace in men over 50 years of age.

REFERENCES

Registrar General's Statistical Review of England and Wales
Part I (Medical)
(1938) No. 18, pp 44–47
(1949) No. 29, Table 10, pp 46–49

Dr L Feinmann

Control of Chronic Infectious Disease

The number of notifications of cases of tuberculosis with a positive sputum in Gateshead falls each year. The total notification rate falls much more slowly. This is because many cases of doubtful activity, of a kind disregarded in the past, are now treated and therefore notified. Some index of infection in the community, other than notification, is needed. Lissant Cox & Hughes (1953) drew attention to this need for a 'live register of infectious cases.' In 1953 there were 276 patients, attending the West End Chest Clinic in Newcastle, 'who are infectious and for whom, in the present state of our knowledge, we have no adequate treatment' (Feinmann *et al.* 1955). This clinic served a population of about 150,000.

In 1956 a similar register was started in Gateshead, which at that time had the highest notification rate in England. 164 names were included: 75 of these had a positive sputum all the time; the remainder appeared incurable because

of repeated relapse and/or extensive disease. Long-term 'good' chemotherapy (Ross 1958) became firmly established between 1954 and 1956 as routine treatment and ample beds were available for treatment or isolation. At the same time sputum culture and sensitivity tests became routine investigations.

In 1957 a special nurse-investigator was appointed to visit and report on this group of patients. Extensive notes were made on the social circumstances and problems presented by each one. Fresh names were added when it was thought that intensive treatment had failed. In all, just over 200 names were collected. Of the original 164 patients, 25 had stopped attending the clinic. Treatment had failed and confidence had been lost. They needed much persuasion to return. Fifty-six patients were readmitted to hospital in the first year and nearly every survivor on the register has had two or three years of chemotherapy. This is in complete contrast to the attitude reported in the past (Feinmann *et al.* 1955) when it was thought that this group had little to hope for from drugs.

As a result of treatment a large number, despite extensive lung destruction, are sputum negative and well. However, by 1960 nearly one-third were dead. Twenty-six had resistant organisms and died of the disease. Of the rest, many were sputum negative for some time before death and pulmonary insufficiency or intercurrent disease was often the cause.

We now think of chronic disease as that presenting in patients who remain sputum positive for two years after notification. Compared with 164 such patients four years ago, there are now 15. Of these, 9 have resistant organisms. All have extensive disease. All were notified before 1954. In addition, each year about 12 patients, nearly all diagnosed before 1954, relapse, having previously been considered cured or quiescent. These are considered to have potentially chronic disease until satisfactory sensitivity tests and response to treatment are obtained. One or two new patients each year will not at first co-operate in adequate treatment. It may be that the partly treated cases of the 1948–54 era will supply further additions to the register.

In the past the causes of chronicity were considered in terms of extent of disease and the social circumstances and behaviour of the patient. It is now clear that inadequate drug regimes are the only important factor. The problem of refusal to take P.A.S. has not in this part of the world, in the last few years, resulted in the appearance of more chronic sputum positive cases. This may be because nearly all new cases are still admitted to hospital and kept there until the disease is reasonably well controlled. On discharge, all patients have two years of drugs but they are informed that intolerance is common and that other preparations are available if the commonly used P.A.S./isoniazid cachets cause upset.

Of 35 patients known to have had organisms resistant to two or more antibiotics, in the last five years, 26 are dead. These figures are similar to those of Stradling & Poole (1959). There has been no evidence in the past five years of new cases developing resistant organisms.

A special effort was made to re-examine contacts of chronic cases. Most were unwilling. 200 were X-rayed but showed no disease. No evidence has been found that newly notified cases have been infected by chronic cases. Many contacts of these patients have had tuberculosis in the past but there was no evidence of active disease in their present domestic contacts.

Professor J Crofton has claimed that with modern chemotherapy no patient need die of tuberculosis and that all can be rendered non-infectious. We have found this so nearly true that we can report its natural corollary – the rapid and substantial decline of chronic infectious tuberculosis. The fears that have been expressed that drug treatment would prolong the lives and therefore the infectivity of this group are not justified. If this progress is continued it seems unlikely that compulsion is ever going to be a necessary part of the treatment of tuberculosis, although strong persuasion is often necessary.

An effort now being made to control the remainder of our chronic cases with some of the newer drug combinations has met with some success.

Contact Examination

In addition to domestic contacts, in the last two years each newly notified patient has been asked to provide a list of close contacts outside the home. A special effort was made to persuade the much increased list of contacts to be examined and if necessary they were brought to the clinic by car. We fall behind the Edinburgh standard of 100% contact examination. 78% of domestic and 70% of other contacts of sputum-negative patients were seen, 87% of domestic and 62% of other contacts of sputum-positive patients. A large proportion of notified contacts have early disease.

X-ray Facilities

Newcastle was a pioneer unit in providing mass miniature radiography (M.M.R.) facilities for the general practitioner. Gateshead doctors used them extensively as they did an X-ray session provided at the chest clinic. Unfortunately, records do not show this usage by Gateshead doctors separately. In 1958, a 100 mm unit was set up in the grounds of the Health Department,

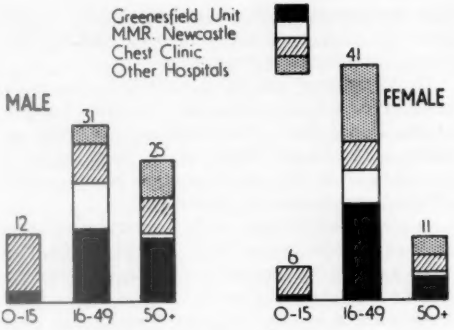

Fig 1 *Tuberculosis notifications in Gateshead for 1960. Age groups and sources of cases*

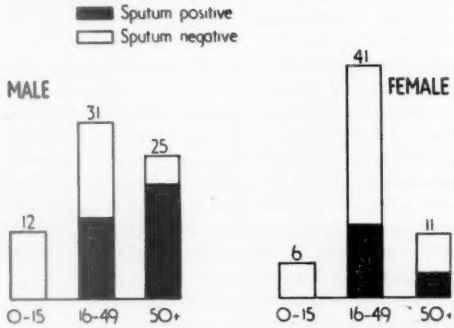

Fig 2 *Tuberculosis notifications in Gateshead for 1960. Age groups and sputum state*

quite separately from the chest clinic. It was intended mainly for general practitioner use but was open to the general public. It was open each afternoon and on two evenings a week. As a result of these examinations 52 cases were notified. The figures for 1960 have not increased despite many appeals. I estimate that its use has doubled the number of Gateshead patients with symptoms who have their chest X-rayed each year. It would not have been possible to manage these numbers with the previous facilities available but it is clear that a unit of this kind does not have the impact of a major mass X-ray campaign.

Other less tangible factors play their part in the control of disease. The lessened fear of disease and the opening of a new attractive clinic two years ago has doubled the number of patients, now 2,000 a year, referred with chest diseases of all kinds, and out of these a small proportion of cases of tuberculosis are found. A separate children's chest out-patient session has been valuable. A quarter of new notifications are made from other hospitals, all too often after a post-operative chest X-ray. This points to the necessity of routine chest films of hospital out-patients, but illustrates how often tuberculosis is diagnosed late. A high proportion of positive cases still have fairly advanced disease.

Fig 1 shows the age groups and sources of pulmonary and non-pulmonary cases notified in Gateshead in 1960 (excluding 5 notifications of pulmonary tuberculosis cancelled due to revision of diagnosis). Fig 2 shows the sputum state of these cases.

REFERENCES
Cox G L & Hughes H F (1953) *Tubercle, Lond.* **34**, 251
Feinmann L, Hurrell G, Taylor M & Woll E J (1955) *Tubercle, Lond.* **36**, 233
Ross J D (1958) *Tubercle, Lond.* **39**, 45
Stradling P & Poole G (1959) *Tubercle, Lond.* **40**, 489

Dr K M Martischnig

During the years 1958–60 an intensive search was attempted for unknown cases of pulmonary tuberculosis in Gateshead. It was felt that the best method for this purpose was to employ the existing Chest Clinic facilities augmented by a new 100 mm Odelca Mirror Camera functioning as a static M.M.R. unit, and by close co-operation with local general practitioners. They were asked to refer all patients attending their surgeries, with not matter what complaint, for chest X-ray. In this scheme special attention was to be paid to men aged 50 and over because of the incidence of newly notified cases in this age group.

Despite all efforts, the scheme failed, largely due to the apathy of the general public. This was especially marked in men in the older age group. Only 2,414 (14·4%) men aged 45 and over out of the estimated number 16,752 (Registerar General's Census 1951) were X-rayed by the Odelca Unit. A scrutiny of general practitioners' record cards in two practices showed that only 38 and 32 men aged 50 and over out of 100 in each practice, had had their chest X-rayed in the past.

During routine clinical work, it was noticed that quite a number of people with active pulmonary tuberculosis gave a history of abnormal chest X-rays in the past. Tuberculosis had been suspected, but after a period of observation considered inactive and supervision discontinued. These then were people, infected by tuberculosis in the past, who finally did break down and require treatment although they seemed to have overcome the original infection, had been symptomless and their intrapulmonary lesions had remained radiologically stable for a considerable length of time. This view was strengthened by information from the M.M.R. unit in Newcastle upon Tyne. To substantiate it further, it was

planned to review 500 cases selected from old records to find out what changes, if any, had taken place and in what time. The criteria for inclusion were: radiologically stable lesion (considered inactive, without previous chemotherapy), and a minimum time lapse of three years from the last X-ray.

Every tenth record of cases discharged from supervision was scrutinized, and if the above criteria applied, a request letter was sent to attend the Odelca Unit for follow-up chest X-ray. Despite a further letter to all who failed to attend in the first instance, out of the 250 who were sent for, only 94 (37·6%) attended; 31 (12·4%) had moved and addresses were not available, and 125 (50%) ignored the request. Of the 94 who attended, only 2 (0·8%) were recalled and large films showed no change, but within three and six months later, 2 men out of the 94 were admitted into hospital with active tuberculous lesions. The survey started in January 1959 and after six months, because of the poor response, it was decided not to pursue this line of investigation any further.

The two causes for the apparent failure were a lack of co-operation on the part of the participants and also a number of cases of active tuberculosis who had abnormal X-rays on previous occasions, had been admitted into hospital since the beginning of the survey. The relevant X-rays, however, were removed from the records on admission into hospital and were not available for inclusion. In view of the latter, it was decided to scrutinize all newly notified cases during 1959. The findings proved important enough to merit the inclusion of 1960 newly notified cases also, to see if these findings could be repeated and if so, what valid conclusions could be drawn.

Fig 1A shows the number of newly notified cases of pulmonary tuberculosis in each year under review, and the total number in the two years. Fig 1B shows the number of cases with abnormal chest X-rays in the past, found amongst all newly notified cases, in each year and in both years combined. Each column is divided into sputum positive and negative cases.

During the years 1959 and 1960, 222 active cases of pulmonary tuberculosis were notified, 100 of which were sputum positive. In 64 (28·8%), previous X-rays showed tuberculous lesions but, as no evidence of activity was found, no antituberculous chemotherapy was given and supervision discontinued. The period between the first abnormal X-ray and the actual breakdown of the lesions varied, the longest interval being nineteen years, the shortest one year, the average four years. In almost every case past X-rays were available and it was possible to compare the original lesion with subsequent development.

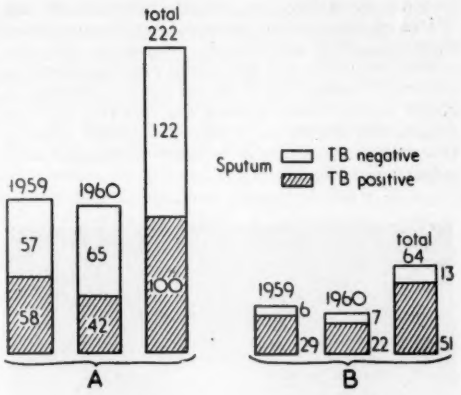

Fig 1 A, *number of new notifications of pulmonary tuberculosis 1959–1960.* B, *number of broken-down radiologically stable lesions.* (*4 cases notified posthumously have been excluded as have 5 that were later cancelled*)

Case report Fig 2 shows a dense lesion in the right upper zone and softer lesions in the periphery in the left upper zone. This X-ray was taken, in June 1955, as a result of M.M.R. findings in a female aged 38, who was an assistant in a fish and chip shop. At the time of examination her symptoms were low backache and loss of 2 lb in weight. She gave a history of bronchitis three or four years previously as the only illness in the past. There was no family history of tuberculosis. The lesions were considered tuberculous, but no clinical

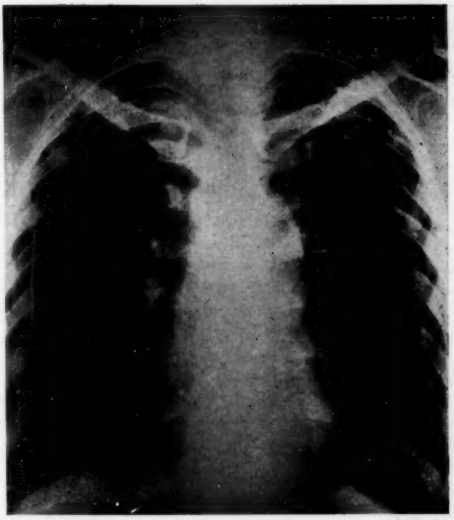

Fig 2 *Miss I H, aged 38 years, 1955*

evidence of activity was found; radiologically the lesions remained unchanged and, after fifteen months, supervision was discontinued. In August 1959 this patient was referred by her general practitioner with a history of two months' illness marked by troublesome cough with abundant sputum and loss of 2 stone in weight. The sputum was positive. An X-ray taken at this time shows extensive bilateral tuberculosis with large cavities (Fig 3).

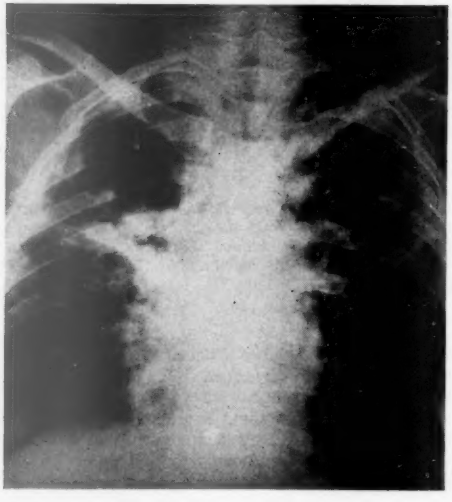

Fig 3 *Miss I H, aged 42 years, 1959*

The sputum-positive cases added to the Tuberculosis Register each year are the important ones. They are the cases searched for to prevent the spread of infection. During 1959 and 1960 there were 100 new sputum-positive cases added to the register and out of these, 51 were cases whose lesions had been considered inactive in the past. 64 cases of tuberculosis were known for years and no treatment was given until they had broken down and 51 of them had become sputum-positive. These 64 cases contributed over one-quarter of all new notifications each year (30·4% and 27·1% respectively), and one-half of all newly notified positive cases each year (50% and 52% respectively).

In the light of these findings and from clinical experience it would appear that 'radiologically stable lesions' will require more than supervision and our findings support very strongly the findings of Hall *et al.* (1960) and the Research Committee of the Tuberculosis Society of Scotland (1958) which indicated that such lesions should be treated.

In establishing the significance of so-called 'radiologically stable lesions' on notifications, a further question arose: what led to the breakdown? In the search for the answer the relationship of age, sex, social and housing conditions, alimentary disorders and drugs was studied. From Fig 4 it is clear that, among men, advancing age was the most important factor, the highest incidence of breakdown being experienced from 55 to 65 years, compared with 25 to 35 years in women. The ratio of men to women was 2·55 : 1. In studying social and housing conditions, no new factors were found. Practically all cases under review fell into social classes V and IV (31 and 32 respectively) and only one in class II. Housing conditions surprisingly did not seem to be important; they were bad in only 4 cases, average in 36 and good in 24. When associated diseases were studied, diabetes mellitus was found in 2 cases. Alimentary disorders were found in 21 cases, 32·8% of all broken-down 'radiologically

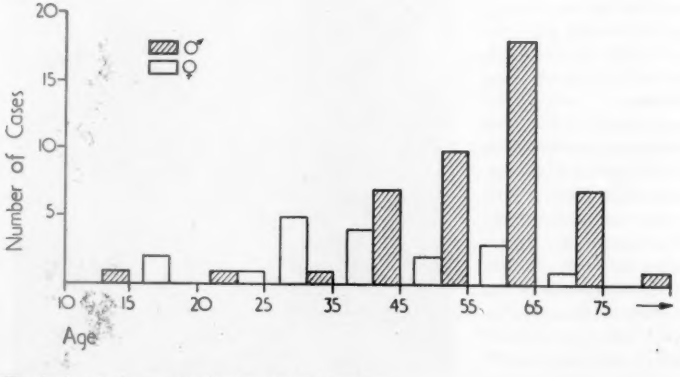

Fig 4 *Age and sex distribution of broken-down radiologically stable lesions*

stable lesions'. In one case the breakdown of a stable lesion was caused by steroids used for the treatment of rheumatoid arthritis.

From this attempt to find out what are the causes of the breakdown of clinically inactive 'radiologically stable lesions', one can postulate that age and alimentary disorders are the main causes, particularly in men. Admittedly the number of cases (64) from which these conclusions are drawn is small, and larger numbers are needed to confirm the factors leading to breakdown.

REFERENCES
Hall Z M, Zorab P A & Jefferson K E (1960) *Tubercle, Lond.* **41**, 47
Tuberculosis Society of Scotland (1958) *Tubercle, Lond.* **39**, 129

Conclusion

Multilateral approaches were made by a team of workers to the problem of tuberculosis in a crowded industrial area. This necessitated regular group conferences, and these were so valuable that it is felt they should remain a feature of anti-tuberculosis work.

How far did the team achieve their task and what was learned in the process? It must be answered that although there was disappointment with some aspects of the study, due to the declining importance of the disease, we learned enough to highlight certain matters. Tuberculin testing of infants and entrant school children involves a large amount of work with very little to show but may nevertheless be worth pursuing for the epidemiological interest. The provision of easily accessible facilities to the patients of the general practitioners is of the greatest importance in detecting the disease at an early stage, and the value of evening sessions is stressed. Similarly, X-ray examination of certain community groups, e.g. domestic and factory contacts and males over 50 with chest illnesses is of equal importance.

The treatment of infectious and non-infectious patients must be more prolonged than the period previously considered to be adequate, and treatment of supposedly inactive tuberculosis will halve the incidence of the infectious cases of tuberculosis, for at least 30% of the newly notified patients had a previous abnormal chest X-ray picture some years before. As preventive measures, contact tracing with the administration of BCG vaccine to non-reactors and the X-ray examination of positive reactors must continue.

We have now returned to the classic machinery of prevention of infectious diseases – the ascertainment, isolation and treatment of cases combined with the supervision and immunizing of contacts – but the members of the team are not in complete agreement about the wisdom of applying compulsory X-ray examination to uncooperative suspects and contacts, whether near or remote.

Acknowledgments

The team engaged in this study included Dr S D Rowlands, Dr L Feinmann and Dr K M Martischnig, chest physicians of the Gateshead Hospital Management Committee area, Dr J Grant, Medical Officer of Health, and Doctors E I Blenkinsop and T L Knaggs, assistant medical officers of the Gateshead County Borough, together with Miss N Wilson SRN. The team is also indebted for help to many of their colleagues in the medical and nursing profession, and especially to Dr W Charles Cockburn of the Public Health Laboratory Service and his colleague Dr C C Spicer.

Meeting March 17 1961

Paper

Problems of Operational Research in the National Health Service
[*Summary*]

by J O F Davies MD (*Oxford*)

Operational research, i.e. the application of scientific method to solving problems of interaction of the parts of an organization in the interests of the whole, is likely to find an excellent field in which to work in the National Health Service, separated as it is into three parts. Reliable factual assessment of what now goes on in the National Health Service is held to be a prerequisite to knowing how to use it to best advantage.

It is suggested that the ascertainment of the needs of the community in terms of medical care must be attempted. The ability to forecast trends would be most rewarding. Morbidity statistics, as now provided by the Hospital Inpatient Enquiry (Ministry of Health & General Register Office 1961), and studies of morbidity in general practice (Logan & Cushion 1958, 1960) should provide information which might help solve certain problems of hospital staffing and bed allocation. A study of the needs of general practice, as being the main provider of medical care, might make the

role of the hospitals and local health authorities clearer. The demands of general practice in terms of radiological and pathological services varies widely. The examination of general practice might be undertaken indirectly by a study of references to out-patient departments. The number of references to hospital varies from 40 (Fry 1959) to 108 (Scott *et al.* 1960) per thousand. In fact these figures relate to practices where the rate is well below average since the number of new outpatients is 12,000,000 per annum from a population of 45,000,000. It is suggested that the whole organization of outpatient services might be reassessed to ensure that it provides what is required.

The determination of inpatient needs in terms of the number of beds to be provided can only be undertaken when a full and efficient outpatient service is provided. A study might usefully be made as to which medical conditions can be treated equally well, or better, in the outpatient department. The duration of stay of patients in hospitals has decreased as pressure of work has risen, though the stay in hospitals is not as short as that in the U.S.A. It is suggested that a study should be made on the effect of short duration of stay in hospital.

The pattern of nursing work on wards appears to be punctuated by crises, making day-to-day variation considerable, so that allocations of nursing staff are for much of the time too much or too little. Would an intensive unit allow most of the wards to operate with a steadier level of nursing work? A careful examination of ward practice before and after the introduction of intensive nursing care as now practised in the U.S.A. might be a valuable piece of research. Other problems for operational research are the optimum size of the nursing unit, the task of the individual nurse, and the shape and subdivision of the ward unit. The problem of communications in hospitals and between hospitals and doctors and in both cases with the patient is a suitable subject for research.

Investigations into co-operative effort between the hospital, general practice and local authority might most usefully come about *via* group practice conducted in purpose-built surgeries. The association of a health visitor, a home nurse, a midwife and appropriate clerical assistance with a group of 4 or 6 general practitioners (one or two of whom were on the staff of the local hospital) catering for a population of 10,000 to 15,000 would make an excellent study and indicate a pattern for future development.

The evaluation of efficiency in medical care is a difficult problem but one well worth undertaking. In this country there have been some outstanding examples such as the confidential review of maternal deaths (Ministry of Health 1960), the B.M.A. Committee on Fractures (1935) and Lee's (1957) work on case mortality in teaching and non-teaching hospitals. But there is a need for continuing or 'built in' evaluations which would determine whether the aims of the particular exercise are really being achieved.

The recent casualty study undertaken by the Nuffield Provincial Hospitals Trust (1960) is an excellent example both of evaluation in efficiency and of operational research. A conceptual framework was constructed against which the performance of a number of hospitals visited was measured. The items considered included the degree of consultant cover, the time spent on casualty departments, the quality of the casualty officer and the status of the department in the hospital. Other factors were the physical facilities available, the degree of consultation with other specialists and the extent to which any preventive action was taken in the light of known local hazards.

[The paper, of which this is a synopsis, will be published, with others, by the Nuffield Provincial Hospitals Trust in a booklet giving an account of a conference in Oxford in December 1960 under the title 'Problems for Operational Research in the National Health Service'.]

REFERENCES

Fry J (1959) *Brit. med. J.* ii, 1322

Lee J A H, Morrison S L & Morris J N (1957) *Lancet* ii, 785

Logan W P D & Cushion A A
(1958) Morbidity Statistics from General Practice. Vol 1; London
(1960) Morbidity Statistics from General Practice, Vol 2; London

Ministry of Health and General Register Office (1961) Report on the Hospital In-patient Enquiry for the Two Years 1956–57. London

Ministry of Health (1960) Reports on Public Health and Medical Subjects. No 103; London

Nuffield Provincial Hospitals Trust (1960) Casualty Services in their Setting: A Study in Medical Care. London

Scott R, Anderson J A D & Cartwright A (1960) *Brit. med. J.* ii, 293

Section of Obstetrics and Gynæcology

President W R Winterton FRCOG

Meeting January 27 1961

Seminar

Pain and Temporary Failure of Function in a Kidney at the Twentieth Week of Pregnancy

M D Cameron FRCS MRCOG (*London*)

The patient was a fit primigravida, aged 19. No significant past history; pregnancy normal until the 21st week when the patient complained of severe, colicky pain in both loins, worse on the right side. The severity became such that she was admitted to hospital. No hæmaturia or dysuria; nausea persistent with occasional vomiting.

On examination: No pyrexia or tachycardia; blood pressure normal. The uterus was enlarged to the size of a 22-week pregnancy and the patient was aware of fœtal movements. The only abnormal finding was marked tenderness in the right loin.

The urine contained a few red corpuscles and epithelial cells, but was bacteriologically sterile.

Hb 76%; W.B.C. 10,700; blood urea 24 mg%.

The most likely diagnosis was thought to be a ureteric calculus which might pass spontaneously. No active treatment was pursued and pethidine 100 mg I.M. controlled the pain. Furadantin was given for five days. Ten days later the pain was no better, more frequent injections of pethidine being required.

An intravenous pyelogram (Fig 1) using only three X-ray exposures showed normal renal function on the left, but no excretion of dye after 45 minutes on the right. There was some nephrogenic effect suggesting an obstructive lesion to the drainage system. No urinary calculi were visible.

A retrograde pyelogram (Fig 2) was then performed. The bladder and ureteric orifices were normal and a catheter was passed 29 cm up the right ureter without obstruction. Copious drainage of clear fluid was obtained. This contained a

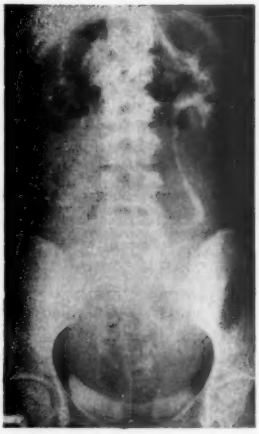

Fig 1 *Intravenous pyelogram at 22 weeks pregnancy*

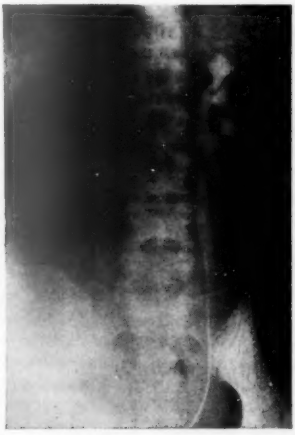

Fig 2 *Retrograde pyelogram [of right kidney at 22 weeks pregnancy (reversed print)*

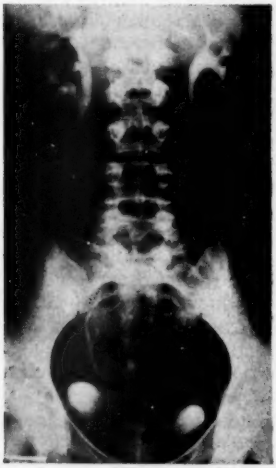

Fig 3 *Intravenous pyelogram 3 months after confinement*

moderate number of white blood corpuscles but was sterile on culture. There was, therefore, no evidence of infection. Injection of diodone revealed moderate dilatation of the renal calyces, pelvis and ureter. There was a kink in the upper ureter but the dilatation persisted below this point, suggesting an obstruction to the ureter in its pelvic course. The catheter was left to drain the renal pelvis but this failed to relieve the patient's pain. Urolucosil was subsequently given for five days.

So much pethidine was now required that the patient was persistently drowsy and yet was never free from pain. There appeared to be three possibilities in the further management of the patient:

(1) Termination of pregnancy: The continued use of large amounts of analgesics raised the danger of addiction. Prolonged ureteric obstruction might lead to permanent renal damage.

(2) Exploration of the kidney: A local lesion, if present, could be dealt with as required. More likely, no abnormality would be found, in which case nephrectomy would be the only solution.

(3) To do nothing and hope the pain would resolve, which involved the risk of prolonged urinary obstruction.

In fact, the last course was chosen but the hoped-for improvement did not occur. The blood urea rose to 51 mg% and the hæmoglobin fell to 50%.

Eighteen days after the first ureteric catheterization, the patient's temperature rose to 102° F. A ureteric catheter was again passed. Pus was obtained, culture of which produced a heavy growth of *B.coli*. The catheter was left *in situ* and the patient was given a course of Furadantin and later tetracycline. The pyrexia continued, and four days later, at the 26th week of pregnancy, premature uterine contractions began. A live male fœtus, weighing 1 lb 12 oz was subsequently delivered but died soon after birth. The blood loss was 4 oz.

The improvement in the patient's condition was dramatic. Within twenty-four hours, there was no pain and no pyrexia. On the fourth day, the ureteric catheter was removed and tetracycline stopped. A 2-pint blood transfusion was given, the hæmoglobin rising to 68%. A catheter specimen of urine showed many pus cells, but was bacteriologically sterile. The patient left hospital on the tenth day after delivery.

Further progress was uneventful. There was no more pain and no urinary symptoms. An intravenous pyelogram (Fig 3) was normal except for a bifid right renal pelvis.

The patient is now contemplating another pregnancy.

I should like to thank Mr Ian Jackson for permission to present this case.

Mr G F Gibberd (*London*) said that he regarded the case as one of pyelitis of pregnancy, and that the unusual manifestations could be looked upon as extreme examples of features which were quite typical of the disease.

Dr A M McCausland (*Los Angeles, U.S.A.*) said he had little to add regarding hydronephrosis and hydroureter in pregnancy except that there was considerable evidence in the literature pointing to the effects of steroids on smooth muscle structures in pregnancy.

Very often there was abnormal dilatation of veins, gall-bladder, kidney pelvis, ureters, bowel, &c., and these dilatations were not entirely due to mechanical obstruction.

Reynolds & Foster (1940) had shown that veins in the ears of rabbits dilated when œstrogen was given. Csapo (1959) and others had shown that œstrogen increased actomyosin in smooth muscle.

It might then be theorized that steroid imbalance could cause dilatation of the kidney pelvis and ureter as was illustrated in the case presented with resultant stasis and infection.

REFERENCES

Csapo A (1959) *Ann. N.Y. Acad. Sci.* **75**, 790
Reynolds S R M & Foster F I (1940) *J. Pharmacol.* **68**, 173

Ovarian Hilar Cell Tumour

E Ch Siganos MB (*London*)

Mrs D D, a married woman aged 40, with 4 children. Menstruation began at the age of 13 and continued normally until it ceased suddenly eighteen months ago. Admitted to Hammersmith Hospital on 12.12.60 because of amenorrhœa for eighteen months and hairiness and deep voice for twelve months. She had had four normal deliveries at term. Sexual life and desire remained normal.

Weight 15 st. Height 69 in. Masculine appearance. Breasts not atrophic. Clitoris enlarged four to five times the normal size. Uterus bulky because of myomata. Ovaries not defined because of obesity.

Investigations: Curettage (March 1960): No curettings. Glucose tolerance test normal. Skull and spinal X-rays normal. Before dexamethasone: 17-ketosteroids 13 mg/24 h, ketogenic steroids – 6 mg/24 h. On the seventh day of dexamethasone 4 mg daily: 17-ketosteroids less than 1 mg/24 h, ketogenic steroids less than 0·5 mg/24 h. Vaginal smear (14.12.60): Cornification Index = 1·5. Androgenic effect.

Retroperitoneal CO_2 insufflation and X-ray showed normal adrenal outlines.

Culdoscopy: Nothing abnormal seen.

Laparotomy (16.12.60): Ovaries macroscopically normal, but section of both ovaries showed the right one to have a small rounded purple-red tumour not visible or palpable from the surface. Adrenals normal to palpation. Right oophorectomy performed. Biopsies taken from the left ovary.

Recovery was uneventful and the patient began to menstruate normally 37 days following the operation.

Acknowledgments: I wish to thank Dr Richard Coe, Professor Russell Fraser, Professor J C McClure Browne and Professor C V Harrison for permission to present this case.

Mr Frank Stabler (*Newcastle upon Tyne*) said that this was a clear case of the sudden onset of masculinity in a 40-year-old woman. He asked why people were so obsessed with the disposition of the abdominal hair as an indication of masculinity? One woman in four had hair growing up to the umbilicus. Hair in the anterior nares, in the ear or on the proximal phalanges of the digits were real evidences of masculinity. Secondly, what was meant by 'Breasts normal'. This was a fat woman and diminution of the amount of *gland* tissue could easily have been missed. Thirdly, what did 'D. & C. normal' mean? Were any scrapings removed and if so what was the histological picture? If not, this was not normal.

He had nothing but praise for the beautiful and simple inductive reasoning that followed. The condition was either due to adrenal abnormality or to ovarian abnormality. Adrenal cortical hyperplasia was rare at such an age and with such a sudden onset but it was possible. Was it an adrenal neoplasm? Presacral air injection with radiography was against any adrenal abnormality and the dexamethasone test was decidedly against an adrenal neoplasm. Her adrenal cortex reacted as does the normal cortex in that the 17-ketosteroids fell to below 4 mg/24 hours. The conclusion was that she had an ovarian lesion. The Stein-Leventhal syndrome was unlikely considering her age and even more because of the marked degree of masculinity and its sudden onset. They were left with one of the rare ovarian tumours though he would have expected a greater 17-ketosteroid excretion. One of his own cases of arrhenoblastoma excreted over 200 mg/ 24 hours. There were really only three masculinizing ovarian tumours though many names were applied to their varying histological appearances:

(1) *Arrhenoblastoma.* This was commonest in the second or third decades and usually there was a palpable lump seldom less than 30 mm in diameter. The histological picture varied from sarcomatous-looking cells to well-formed cords like seminiferous tubules.

(2) *Masculinovoblastoma.* This was butter yellow in colour and on histological section showed ballooned cells full of fat very like the cells in adrenal cortex (though it must not be taken for a piece of adrenal cortex). The only case he had had was in a woman in the early 20s.

(3) *Hilus cell tumour.* In the normal ovary of normal women it was not uncommon to find a collection of cells in the hilus looking like the interstitial Leydig cells of the testis even to the presence of Reinke albuminoid crystals. Tumours of these cells were associated with the onset of masculinity.

As the clinical account divulged that Professor McClure Browne needed to split the ovary to find the tumour the last was the most likely diagnosis and Mr Stabler congratulated him on relying so firmly on the preceding investigation that he went to this length to reveal the tumour. He did, however, let himself down a little by doing culdoscopy. If culdoscopy showed an ovarian tumour he was going to open the abdomen. If it did not he was still going to open the abdomen so why take the trouble?

Professor J C McClure Browne (*London*) said that they were much indebted to Mr Frank Stabler for the able way in which he had clarified the problem of virilism. In this case it was quite clear from the investigations that a virilizing ovarian tumour was to be suspected, though pelvic examination failed to reveal any suggestion of ovarian enlargement. As Mr Stabler had pointed out, the use of the culdoscope in this case could well have been avoided as laparotomy was clearly indicated. However, in the past few years, through the courtesy of Professor Russell Fraser of the Department of Endocrinology at Hammersmith, Professor McClure Browne had had the privilege of seeing many cases of virilism, and had found that the culdoscope in these cases was a useful diagnostic weapon. It was largely in the hope of actually seeing a small ovarian tumour that it was employed in this case, though in fact the ovaries were not seen. At laparotomy both ovaries appeared normal and moreover felt normal. There was no palpable tumour. Nevertheless it seemed best to split both ovaries. The split left ovary appeared entirely normal, but on splitting the right ovary the small brownish rounded area was immediately apparent.

Professor McClure Browne thought it was Mr Stabler who had said that the harsh masculine type of voice was rarely improved after operation. In this case the patient's voice had been recorded before operation, and again a month afterwards, and there was a noticeable change for the better.

Professor C V Harrison (*London*) said that he had received a biopsy specimen of the left ovary measuring $20 \times 15 \times 5$ mm. It contained one follicle with an extremely thin theca. No corpus luteum was found. The right ovary measured $30 \times 20 \times 20$ mm with a buff-coloured tumour mass 15×20 mm, consisting of solid sheets of cells without any special arrangement. There was minimal stroma of reticulin fibrils and small vessels. The cells were uniform, round or polyhedral, about 15μ in diameter, with a central nucleus containing a small nucleolus. The cytoplasm was eosinophilic and resembled ground glass. In frozen sections there was some lipid present but this was patchy. Reinke albuminoid crystals were demonstrated. On these data the diagnosis of hilar cell tumour of the ovary appeared justified.

Meeting February 24 1961

Discussion on the Cervix – Ante-partum and Post-partum

Professor H C McLaren (*Birmingham*)

I propose to open this discussion with a re-appraisal of what is the limit of normal in the cervix.

As part of an assay of the value of aspiration cytology tests as compared to the method of scraping the cervix for cell-specimens my colleagues, M J D Noble, F Selby Tait, A L Easton, E M Little and I have completed 5,000 speculum examinations mainly at an early stage in pregnancy.

At speculum examination in early pregnancy there is no 'textbook' appearance. The most common finding is a thick opaque mucous plug at the external os. Removal of this very often shows an 'erosion' of variable size, sometimes flat and obviously innocent from the clinical point of view but on occasions the appearance at the lower cervix, combined with a marked tendency to bleed on the most gentle mopping, raises clinical suspicion of carcinoma.

The time-honoured term to describe these 'raw' red areas on the cervix is an erosion. The term is a poor one since it conjures up a process of 'erosion' or ulceration, which is far removed from the histological picture. For example, a simple punch biopsy through the squamo-columnar edge of an erosion will commonly show no more than a descent of columnar epithelium, while postnatal involution leads to a marked diminution or the complete disappearance of these columnar epithelial areas. All this was described fifty years ago by Robert Meyer (1910), who referred to the epithelium at the portio as 'tidal epithelium'. I think the time has now come to use a new descriptive term. How would my colleagues in obstetrics and pathology consider the term 'PENCE' (Physiologically ectopic normal columnar epithelium) for pregnancy erosions? These lesions, it should be noted, are mainly asymptomatic and must be distinguished from the infected gynæcological 'erosion' which produces columns of mucopus; for this pathological clinical entity one uses justifiably the gynæcological term 'infected erosion or cervicitis' – a cause of mucopurulent discharge, i.e. *symptomatic* and requiring treatment.

Postnatal Erosions (*PENCE*)

How frequently PENCE or physiological erosions remain after delivery is not known but many do persist and indeed in some form they may be a permanent condition of the cervix. They are, of course, common in the gynæcological clinic (25% in our department).

In a report on 121 patients with postnatal erosion and 141 with normal cervices we came to the following conclusions (McLaren 1952):

(1) Postnatal erosions are commonly asymptomatic and may resolve or involute without treatment.
(2) Postnatal erosions can be a source of *mucorrhœa:* but in our series treated by simple observation only 9% finally required cauterization.
(3) Squamo-columnar biopsies from normal cervices and postnatal erosions are often so alike microscopically that they cannot be differentiated. Inflammatory reaction of some degree is common to both, i.e. subepithelial leucocytes and a degree of vasodilatation in the stroma is seen in both and must be accepted as part of normal involution.

Fig 1 summarizes our experience with simple observations of postnatal erosions. Observation (with no treatment) of 77 postnatal erosions left us

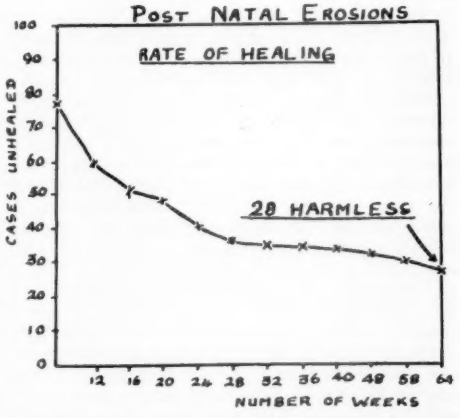

Fig 1 *The disappearance of cervical erosions or 'PENCE' without treatment was observed in most cases by about the sixth month. The remainder were simply observed and treated only if shown to be a source of mucorrhœa. Only 7 erosions out of the original 77 were finally cauterized for mucorrhœa, the remainder were labelled as 'harmless' and asymptomatic*

with 30 erosions but these were mostly very small and asymptomatic, i.e. of the initial 77 erosions or PENCE only 7 (9%) gave rise to mucous discharge for which cautery was required. The following case report gives an example of our conservative approach:

Mrs A, aged 25, para 1. Asymptomatic erosion over most of the posterior lip of the portio cervicis vaginalis.
Treatment: Observation only – at several tests spermatozoa were detected in the cervical mucus.
Result: In due course conception, with a persistence of her asymptomatic erosion which was observed through her second pregnancy to the ensuing puerperium (McLaren 1957).

The prevention of cancer by cautery: The writings of Cashman (1945), and more recently those of Younge & Kevorkian (1959), have kept before us the theoretical possibility of reducing the prospect of carcinoma in the individual by deep thermal burning of the lower cervix. If we accept the Younge-Cashman prophylactic theory we should apply the cautery not only to the cervix with an erosion but to the cervix with none for there is no evidence that an erosion predisposes to carcinoma.

Finally, the student of fertility will make a plea for cauterization well short of scarring or stenosis of the canal, for healthy mucus secretion at the time of ovulation is one of the links in the chain leading to conception.

My personal view is that deep thermal destruction of the lower cervix has not been shown clearly to prevent cancer in the individual or in the community and I do not use the cautery for this purpose.

In summary, the incidence of erosions in our gynæcological clinic is 25% and in our antenatal clinic at least 20%. I make a plea for the simple observation of postnatal erosions for most of them disappear or become small and innocuous. It is an important aspect of teaching that erosions (or PENCE) are usually part of pregnancy and that, as in the gynæcological clinic, only a few symptomatic erosions require any form of treatment.

Carcinoma-in-situ in Pregnancy

Since 1952 in our department all gynæcological outpatients have been screened by the technique of vaginal cytology, the test being carried out as part of an ordinary gynæcological examination. It is not our practice to tell patients (unless they are nurses or medical colleagues), that the test is being carried out and very few lay patients, in fact, know that the test has been done. We are now satisfied that clinically normal cervices if 'searched' by the technique of cytology will prove to have carcinoma-in-situ in about 4 per 1,000 patients, and to that we can add 1 per 1,000 with a small undetected invasive carcinoma, a total of about 5 per 1,000. Carcinoma-in-situ is curable whereas carcinoma may or may not be, but whether the clinician considers the effort of screening patients to be worth while turns on the prophylactic value of removing carcinoma-in-situ.

It has been shown clearly by Petersen (1955) that, left untreated, carcinoma-in-situ of the cervix may develop into invasive (metastasizing) carcinoma, i.e. alter its nature so that at some point in time in the future, perhaps two, five or even fifteen years ahead, the patient may die of carcinoma cervicis. Secondly, Erickson *et al.* (1956) and Fidler, Boyes & Lock (1957) are collecting evidence from vast field surveys which give a very strong hint that the removal of carcinoma-in-situ significantly reduces the incidence of carcinoma. We have not yet the absolute proof but the work of Petersen, Erickson and Boyes seems to point clearly to the prophylactic value of the removal of carcinoma-in-situ.

The position in our department at the moment is that we know the scope of the technique of cytology as part of a diagnostic service in the hands of a team of clinicians, an expert pathologist and trained cytologists. We have 'searched' various groups such as gynæcological outpatients and diabetics (Noble & Attwood 1958). We have now applied the technique to the pregnant woman, aware that this group is on average somewhat younger than our gynæcological patients (Table 1).

Table 1
Results

Total consecutive antenatal patients	5,000	
Positive or 'suspicious' smears	60	
Proven carcinoma-in-situ or micro-carcinoma	9	16
Invasive carcinoma (already suspected clinically)	1	
Awaiting admission: strongly positive smears thought to arise in carcinoma-in-situ	6	

Thus to date we have revealed in the normal pregnant cervix 'pathology' in 9 and we feel fairly sure that in this group of 5,000 the total will be 15 (about 3 per 1,000) which compares with our 4 per 1,000 in gynæcology. The single case of carcinoma is not included since it was a confirmatory positive smear, i.e. from a cervix thought to be worthy of biopsy on clinical grounds.

But there is more: of the 60 positive or sus-

picious smears 44 are certainly worthy of clinical and cytological follow-up. This group may in fact prove to be of greater interest than the ascertaining of the incidence of carcinoma-in-situ as detected by cytology, for in this 'cytological' group Miss M E Attwood and her team have shown a movement of cells which may be described as a movement towards and away from 'malignancy'. This will be reported at a later date but at the moment we can see a question which must be faced: is this group of patients labelled in pregnancy by cytology likely to produce carcinoma-in-situ at some future date? Have we our first hint? There is in this question an obvious challenge to research.

Clinical handling of 'positives': As part of a long-term programme of investigation our group are in the process of assessing the value and safety of cone biopsy or conization of the cervix (1) as a means of diagnosing carcinoma-in-situ and (2) as a means of permanent cure of the lesion. To date about 70% of our cases of carcinoma-in-situ have been 'coned' and subjected to careful follow-up without recourse to hysterectomy (McLaren 1960). The therapeutic problem in pregnancy is different, for we must if at all possible preserve the fœtus. In the process of our search for carcinoma or carcinoma-in-situ we may, however, have precipitated two abortions by ring biopsy. The first, perhaps as a result of a damaged internal os cervicis, followed thirteen weeks after the conization which proved carcinoma-in-situ to be present. The second abortion followed a second ring biopsy in a patient aged 28 who in her second pregnancy developed a bleeding warty mass on her cervix which we could not differentiate from carcinoma without biopsy. Although the smears were reported by the cytologist as negative yet we felt that nothing short of a flat cone biopsy was justified if the safety of the mother was to be given proper consideration. Whether as a result of this second modified cone biopsy or not she aborted within ten days. The tissues showed nothing pathological at histological examination so that in retrospect we regretted the ring biopsy.

Our policy varies somewhat among members of the clinical team but may be summarized as follows: Following a positive smear, if there is no clinical evidence of carcinoma, i.e. if the pregnant cervix remains clinically normal, we allow delivery at term and readmit the patient for formal cone biopsy soon after delivery. Our experience in the Midlands, however, with pregnant patients is that readmission is not always easy to arrange; the young mother with her newborn child is very likely to refuse or repeatedly postpone her admission. We have in this a real problem in the handling of the patient with cytological evidence pointing to carcinoma-in-situ. So far, however, we have had no disasters such as the belated discovery of carcinoma but we wish to emphasize that this 'pregnancy' group may be very difficult to handle and in this they contrast with our gynæcological patients to whom we apply the following: a positive smear ⟶ perhaps a repeat smear ⟶ if again positive ⟶ cone biopsy ⟶ histology ⟶ carcinoma-in-situ ⟶ prolonged and careful follow-up ⟶ if again a positive smear ⟶ simple hysterectomy. Such a routine, of course, cannot be applied in pregnancy where the obstetrician must not endanger the life of the fœtus for the removal of tissue which is only *potentially* lethal and then only in a few months or years. In a personal communication R R Greene of Chicago and D A Boyes of Vancouver state that with their pregnant patients they have pressed the taking of cone biopsies for positive smears but a considerable number of abortions have resulted. It has to be remembered, however, that carcinoma-in-situ is a potential source of invasive carcinoma and moreover certain biopsies showed evidence not only of carcinoma-in-situ but also micro-carcinoma or even frank carcinoma. How far to press for histology following a positive smear in pregnancy is obviously a difficult problem; no one at our present state of knowledge can lay down rules to cover every patient. At the moment we can report that we are pressing on carefully with a conservative policy linked with meticulous clinical and cytological follow-up studies.

In summary, 5,000 consecutive patients screened by cytology gave an incidence of carcinoma-in-situ of about 2 per 1,000; when histology for all patients is available the figure is likely to be 3 per 1,000. The incidence of 'suspicious' smears is 12 per 1,000 and this group is the subject of a follow-up study.

Acknowledgments: I wish to thank my colleagues in the Department of Obstetrics and Gynæcology of the University of Birmingham, and the Birmingham and Midland Hospital for Women; also the Birmingham Branch of the British Empire Cancer Campaign for financial assistance.

REFERENCES

Cashman B Z (1945) *Amer. J. Obstet. Gynec.* **49**, 190
Erickson C C, Everett B E jr, Graves L M, Kaiser R F, Malmgren R A, Rubel, Schneier P S, Cutler S J & Sprunt D H (1956) *J. Amer. med. Ass.* **162**, 167
Fidler H K, Boyes D A & Lock D R (1957) *Canad. med. Ass. J.* **77**, 79
McLaren H C
(1952) *Brit. med. J.* **i**, 347
(1957) *Med. Pr.* **237**, 207
(1960) *Acta Un. int. Cancr.* **16**, 385
McLaren H C, Taylor C W & Attwood M E (1958) *Lancet* **i**, 398
Meyer R (1910) *Arch. Gynäk.* **91**, 529
Noble M J D & Attwood M E (1958) *J. Obstet. Gynæc., Brit. Emp.* **65**, 64
Petersen O (1955) *Acta radiol. Stockh.* Suppl. 127
Younge P A & Kevorkian A Y (1959) *Ciba Foundation Study Group*, London; No. 3 p 83

Miss M E Attwood (*Birmingham*)
We have already reported on the use of exfoliative cytology in the gynæcological clinic as a method of searching for carcinoma-in-situ (McLaren *et al.* 1956, 1958). In many centres abroad it has become a routine laboratory procedure known to find 3 or 4 cases of carcinoma-in-situ in every 1,000 patients as well as the occasional case of invasive carcinoma.

Findings
Five thousand consecutive antenatal patients have been screened; all have had cervical scrapes (Ayre 1947) and 1,500 have also had simultaneous vaginal aspirations. Smears were taken at the patient's first visit to the clinic between the 8th and 12th week of pregnancy.

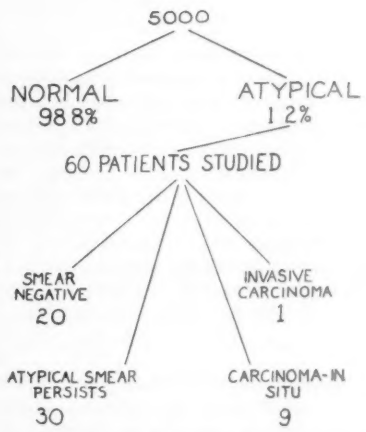

Fig 1 *Five thousand antenatal patients produced 1·2 % atypical or positive smears. Ten patients had histological investigations and 30 continue to show atypical cytology. In 20 patients smears have become negative*

Cytology showed that 5% of antenatal patients had trichomonas infection; 8% had monilial infection. In contrast, of 16,000 gynæcological patients, 26% had vaginal trichomonas infection and only 2% monilial infection.

In our series of patients 60 have had smears labelled as positive or suspicious, i.e. cells were present with obvious dyskaryosis or with changes which we label as malignant although we are quite aware that this does not mean carcinoma in the patient. An attempt has been made to follow up all patients. We have divided our cytological groups into two: (*a*) Those placed under close clinical and cytological investigation, and (*b*) those considered to require histological investigation (Fig 1).

Six patients have had more than one pregnancy during our three-year observation period. Three of these produced suspicious smears during pregnancy which became negative when the patient was delivered and remained negative during the next pregnancy. On the other hand, 3 patients who had had suspicious smears, which became negative postnatally, again produced atypical cells during the next pregnancy. All 6 patients are under close clinical observation.

Two patients had postnatal smears which became negative and remained unaltered for two years. Without further pregnancies they have become positive: carcinoma-in-situ was found in both (Fig. 2).

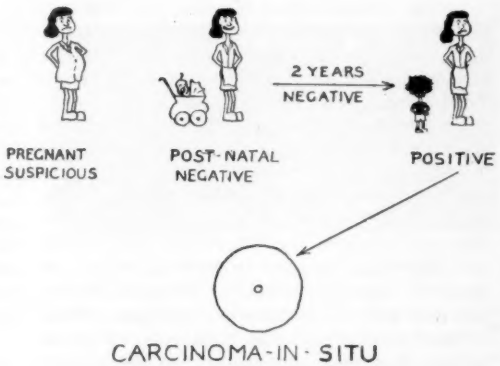

Fig 2 *A patient may have a smear which becomes negative postnatally but she must be watched over an indefinite period against the possibility of a future carcinoma-in-situ*

REFERENCES
Ayre J E (1947) *Amer. J. Obstet. Gynec.* 53, 609
McLaren H C, Taylor C W & Attwood M E (1956) *J. Obstet. Gynæc. Brit.Emp.* 63, 801
(1958) *Lancet* i, 398

Professor W C W Nixon (*London*)
The investigations of Hughesdon (University College Hospital), Dr and Mrs Harkness (University College) and Danforth (Northwestern University Medical School, Chicago) have revealed the cervix in obstetrics to be something more than just the lower end of the uterus. They have studied mainly the muscle, collagen, and cement substance. The epithelium has received scant attention. Moricard & Cartier (1956) in Paris examined the cervix in 1,000 pregnant women by colposcopy, cytology, Schiller test, and biopsy. Their findings on colposcopy showed the

cervix to be normal in only 140 patients (*see* Table 1).

Table 1
Examination of 1,000 pregnant women by colposcopy and biopsy (Moricard & Cartier 1956)

Colposcopy		*Biopsy*	
Normal cervix	140	Acute inflammation	23
Cervicitis	70	Simple dysplasia	92
Extroversion	447	Squamous dysplasia	58
Isolated 'transformation' zone	149	Leukoplakia	15
Iodonegative	75	Dysplasia to be watched	8
Extroversion with iodonegative zones	112	Irregular nuclei dysplasia	5
Corrugated zones	2	Intra-epithelial carcinoma	9
Polyps	5		

The high incidence, nearly 1%, of intra-epithelial carcinoma is striking.

At the Boston Free Hospital for Women, Friedell *et al.* (1960) found in 235 cases of carcinoma-in-situ of the cervix that 2·6% of the patients were either pregnant or had just terminated a pregnancy when the diagnosis was made. From the Boston Lying-in Hospital, Johnson *et al.* (1959) examined the cervix in pregnancy and during the postpartum period for the frequency of clinical erosions and of Schiller-positive areas. They found that 60% (254 cases) had clinically abnormal cervices. The first delivery had a small but significant tendency to produce erosion of the cervix whereas subsequent deliveries did not. Erosions were more common in younger women. In multigravidæ erosions both pre- and postpartum were significantly lower in the patients who had been cauterized prior to the current pregnancy.

It might appear, therefore, that there is a correlation between pregnancy and carcinoma-in-situ. However, present opinion is that pregnancy does not influence the rate of growth of this disease but that marriage at an early date, before the age of 20, is a factor in its development.

Exfoliative Cytology

Ideas are often generated in this country but regrettably are not always implemented so that others get the credit. Let us not forget that it was Dudgeon, Bamforth and Wrigley of St Thomas's Hospital who were the first to detect cancer by exfoliative cytology. There is still resistance and apathy in this country to the employment of this method for screening the female population for genital cancer. A report on 608,000 cytological examinations – the largest series in the world – has been published by the National Cancer Institute in U.S.A. (Kaiser *et al.* 1960). From this it has been concluded that in every 100,000 women there exist about 245 who have intra-epithelial cancer of the cervix and 150 who have invasive cancer. Thus the prevalence rate (in-situ and invasive) is 3·95 per 1,000.

It is ironical that a health, or rather a disease, service, that spends hundreds of millions of pounds a year cannot afford to make more readily available on a national scale a cytological service which would, by early diagnosis of cervical cancer, reduce very considerably the cost of this disease in mortality, misery and money. As Beecham & Andros (1960) have stated, 'there seems to be enough carcinoma of the cervix in younger women, especially those bearing children, to warrant the routine use of vaginal smears in pregnancy. In addition to those patients found to have cervical malignancies there are those with basal cell hyperplasia who should be watched carefully for a possible progression of this lesion to malignancy'.

The Schiller Test

This simple and inexpensive test will exclude anaplasia and carcinoma-in-situ as frequently as the special tests such as biopsy and cytology. If the squamous epithelium is stained dark brown (Schiller-negative) by iodine, it can safely be concluded that the histology is normal. Nyberg *et al.* (1960) found in 313 cases with Schiller-positive (iodine-negative) spots that there was atypical histology (moderate and pronounced atypia, carcinoma-in-situ, invasive carcinoma) in 19%.

This test should be made an obligatory part of a postnatal examination if cytology is not available.

The Future

It will be by biochemical and biophysical means that we shall have to tackle the problem of cancer of the cervix. Enzyme studies of the vaginal fluid by Lawson (1959), involving the estimation of glucuronidase and mannosidase, indicate the wind of change in our research. There will be other enzymes that need to be studied. The deoxyribose nucleic acids (RNA and DNA) in the cytoplasm, nucleolus and nucleus are key substances and their variations need to be detected early. Already it is claimed that this is possible by fluoroscopy and the acridine orange dye and that this method is as accurate as cytology and cheaper and quicker. This line of investigation is worthy of more study.

The Challenge

In 1959 in England and Wales 0·99% (1 in 100) of deaths among women from all causes were due to cancer of the cervix and 5·6% (1 in 18) of all cancer deaths were due to this disease. These are depressing figures. The delight that flows from a Wertheim hysterectomy operation is satisfying to the surgeon but not to the patient, and the optimism of the radiotherapist is not the answer for the permanent cure of cervical

cancer. As gynæcologists we have a very special challenge, namely, to discover the cause of cancer since the cervix unlike other parts of the body is readily accessible for biological study. Cancer of the cervix is a preventable disease. Life and the cervix are in our hands.

REFERENCES
Beecham C T & Andros G J
(1960) *Obstet. Gynec., N.Y.* **16**, 521
Danforth D N, Buckingham J C & Roddick J W
(1960) *Amer. J. Obstet. Gynec.* **80**, 939
Friedell G H, Hertig A T & Younge P A
(1960) Carcinoma in situ of the Uterine Cervix. Oxford
Harkness M L R & Harkness R D (1959) *J. Physiol.* **148**, 524
Hughesdon P E (1952) *J. Obstet. Gynæc., Brit. Emp.* **59**, 763
Johnson L D, Sheps M C & Easterday C L
(1959) *Obstet. Gynec., N.Y.* **14**, 452
Kaiser R F, Bouser M M, Ingraham S C & Hilberg A W
(1960) *Publ. Hlth. Rep., Wash.* **75**, 423
Lawson J G (1959) *J. Obstet. Gynæc., Brit. Emp.* **66**, 946
Moricard R & Cartier R
(1956) *Bull. Féd. Soc. Gynéc. Obstet.* **8**, 314
Nyberg R, Tornberg B & Westin B
(1960) *Acta obstet. gynec. scand.* **39**, 540

Mr Dennis G Bonham (*London*)
The extensive study of the cervix uteri on 853 operation and necropsy specimens by Kaufmann and his co-workers (Kaufmann & Ober 1959, Hamperl & Kaufmann 1959) has shown important variations in the incidence of cervical 'erosion' or 'eversion' with age. The latter term is preferred and used subsequently to refer to the presence of columnar epithelium on the portio vaginalis. Kaufmann's observations suggest that columnar epithelium appears temporarily on the portio surface during active reproductive life.

It is suggested that the cervical erosion or eversion of young women is related to an increased volume of the cervix related to endocrine change, a view originally proposed by Bourne (1940) and Bond (1940) at a meeting of this Section. Epperson *et al.* (1951) showed by biopsy an incidence of erosion or cervicitis in over 50% of pregnant cervices antepartum and persisting after delivery. An erosion incidence of 264 of 277 pregnant cases by biopsy is reported by Hamperl *et al.* (1954).

Speculum examination, Schiller tests and biopsies in pregnancy and postpartum are reported by Johnson *et al.* (1959) in 250 cases. Some 60% of patients had erosions or Schiller-positive cervices ante- or post-partum. A negative relation of erosion incidence to age was the most significant finding.

Following the publication of the extensive work of Kaufmann on the removed uterus, described above, we at University College Hospital began an intensive study of the cervix in pregnancy and afterwards.

Methods of Study
Available methods of cervical study include speculum examination, colposcopy, colpomicroscopy, cytology, biopsy and possibly the estimation of the enzymes in the vaginal fluid as described by Lawson (1959). To these may be added the use of vital staining techniques, the best known being Schiller's iodine.

In our series the simplest methods have been used initially, comprising speculum examination with a 'Coldlight' speculum, precautions being taken to avoid distension opening the cervical canal; the Schiller's iodine test as described by Younge (1957); when the latter has been positive, a punch biopsy has been taken, using Cushing's pituitary punch forceps (Fig 1) followed by cautery hæmostasis.

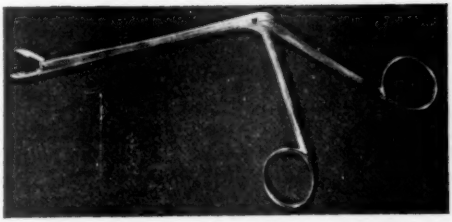

Fig 1

The same patients were examined at 16 and 36 weeks of pregnancy and again at the postnatal clinic six to eight weeks after delivery. Results are recorded diagrammatically, one circle being used for the appearance of the cetrimide-cleaned and dried cervix, and another for the appearance after the application of Gram's iodine solution (iodine 2 g, potassium iodide 4 g and water to 600 ml).

The eversions have been classified as follows: *Minimal*, a small visible rim of columnar epithelium. *Small*, patches on either or both lips or a disc around the os less than half the area of the portio. *Moderate*, covering about half the area of the portio. *Large*, covering two-thirds or more of the area of the portio.

Results
Our early results are shown in Table 1. Of the 200 patients seen at 16 weeks, 68% had some cervical eversion. This incidence is in accordance with the results of the other workers. The mean age of our patients was 27·5 years and an interesting breakdown by age is shown in Table 2 where the patients are divided at 28 years. In the younger patients there was a higher incidence of eversion of each type and the total figures of 75% and 61% are significant by the χ^2 test at a level of $p=0{\cdot}05$.

There is good agreement with the figures of Kaufmann and Johnson. A similar distribution by parity was made and here the findings in Table 3 show a higher incidence in parous women both overall and in each size group excepting the minimal eversion.

Table 4 shows an analysis by age and parity. The significant difference between and incidence of eversion of 80% in parous patients under 28 years and 50 % in the nulliparæ over 28 years, is clearly shown.

Table 1
Incidence of eversion (%) at 16 and 36 weeks antepartum and at the postnatal clinic (P.N.C.)

Cases	Exami-nation	No eversion	Total eversion	Mini-mum	Small	Moderate	Large
200	16 wks	32	68	11	29	19	9
72	36 wks	28	72	12	18	28	14
52	P.N.C.	43	57	15	25	15	2

Table 2
Incidence of eversion (%) at 16 weeks, by age groups

Cases	Age	No eversion	Total eversion	Mini-mum	Small	Moderate	Large
106	Under 28	25	75	13	31	22	9
94	28 and over	39	61	10	27	16	8

Table 3
Incidence of eversion (%) at 16 weeks, by parity

Cases	Parity	No eversion	Total eversion	Mini-mum	Small	Moderate	Large
107	Nulli-paræ	35	65	16	25	16	8
93	Parous	28	72	6	33	23	10

Table 4
Incidence of eversion (%) at 16 weeks

	Under 28	28 and over	Overall
Nulliparæ	72%	50%	64%
Parous	80%	68%	72%
Total	75%	61%	68%

Thirty-six weeks: There was an increase in the number, size and thickness of erosions, and the results in the 72 patients so far followed are shown in Table 1. We preferred to follow the same patients throughout, rather than take sample groups of patients in the manner of Johnson. Table 5 column (*a*) shows the figures obtained by comparing the cervix at 16 and 36 weeks by assessing an increase of eversion size on the classification scale (a worsening), a decrease (or improvement) or no change.

Table 5
Change in appearance of cervix (%) during pregnancy, 16–36 weeks, and after delivery 16 weeks or 36 weeks to postnatal clinic

	(*a*) *16/36 weeks*	(*b*) *16/P.N.C.*	(*c*) *36/P.N.C.*
No change	56	48	40
Worse	37	14	10
Better	7	38	50

Postnatal examination: Here the numbers are smaller but the general incidence was similar to that in a larger group seen postnatally only. Table 1 gives the incidence of eversion in the 52 patients, which has fallen to 57% overall. A more striking postpartum improvement is brought out by the better, worse, or no change assessment, but here we can compare the postnatal examination with both the 16- and 36-week appearances. The most marked improvement is from the 36th week to the postnatal examination. Both results are shown in Table 5, columns (*b*) and (*c*).

These results suggest that parturition is not in any way responsible for the postpartum eversion. The part played by pregnancy cannot be assessed until there is a comparable study in normal non-pregnant women of a similar age group distribution.

Schiller tests: Six patients at 16 weeks (3%) had positive Schiller tests, and 6 others cervical polypi. In each case biopsy showed essentially normal findings. Two biopsies at the postpartum examination were also negative.

Discussion

In this preliminary study the high incidence of erosion in pregnancy is well shown, together with the interesting age relationship. Further work, particularly on unselected non-pregnant patients, would be of value in assessing how far the erosion of young women is related to pregnancy.

The natural history of the cervical erosion at present unfolded is such that the six-week postpartum cauterization championed over the years by Professor F J Browne (Browne & Browne 1960) is not justified and the waiting policy of Professor McLaren (1952) should be adopted.

A large population-screening survey, involving 10,000 women, by the Department of Obstetrics and Gynæcology at Peking Union Hospital and Peking Obstetrical and Gynæcological Hospital (1960) has shown the incidence of carcinoma-in-situ to be 5·4 times higher in eroded than in normal cervices. This may be related to the easier detection of carcinoma-in-situ in eroded cervices by cytology rather than when the dangerous zone is endocervical. One therefore feels that, at present, treatment of erosions should be limited to patients who have symptoms (Ross 1950).

Records over many years will be needed to solve the problem of greater cancer liability in eroded cervices, and we are now establishing a register of well-recorded cervices.

Schiller tests and biopsy of the cervix in the clinics appear to be entirely satisfactory except at 36 weeks when they are technically more difficult and unnecessary.

The question of the early diagnosis of carcinoma-in-situ naturally arises. In this series the mean age was over 27 – approaching the mean age of incidence of carcinoma-in-situ reported by Johnson (1960) as 32·6 years at Boston.

As obstetrician-gynæcologists we have both a great responsibility and a unique opportunity of screening our patients. Ultimately cytology will probably be the answer but until facilities are universally available one feels that more use should be made of Schiller tests and biopsy at 16 weeks and in the postnatal clinic.

REFERENCES
Bond L T (1940) *Proc. R. Soc. Med.* **33**, 788
Bourne A W (1940) *Proc. R. Soc. Med.* **33**, 787
Browne F J & Browne J C McClure (1960) Antenatal and Postnatal Care. London; p 414
Department of Obstetrics and Gynæcology, Peking Union and Obstetrical and Gynæcological Hospital (1960) *China Med. J.* **80**, 459
Epperson J W W, Hellman L M, Galvin G A & Busby T (1951) *Amer. J. Obstet. Gynec.* **61**, 50
Hamperl H & Kaufmann C (1959) *Obstet. Gynec., N.Y.* **14**, 621
Hamperl H, Kaufmann C & Ober K G (1954) *Arch. Gynäk.* **184**, 181
Johnson L D (1960) *New Engl. J. Med.* **262**, 3
Johnson L D, Sheps M C & Easterday C L (1959) *Obstet. Gynec., N.Y.* **14**, 452
Kaufmann C & Ober K G (1959) *Ciba Foundation Study Group*, London: No. 3 p 61
Lawson J G (1959) *J. Obstet. Gynæc., Brit. Emp.* **66**, 946
McLaren H C (1952) *Brit. med. J.* i, 347
Ober K G (1961) Personal communication
Ross J R W (1950) *Brit. med. J.* ii, 647
Younge P A (1957) *Obstet. Gynec., N.Y.* **10**, 469

Mr D J MacRae (*London*) said that an important aspect of exfoliative vaginal cytology was its ability to monitor the progesterone/œstrogen ratio by examination of cell morphology and estimation of the cornification index (C.I.). The pattern of the progestational smear had been described and the low level of the C.I. given for normal pregnancy (Spira & MacRae 1960). The use of vaginal cytology had been extended to the various pregnancy complications. It was common for patients, referred for a hormone implant because of previous abortion, to have a normal smear in the present pregnancy; they were thus not in need of hormone treatment. Where a hormone implant was necessary, further smears would show if progesterone dominance was satisfactory; oral or intramuscular hormone therapy over a short period might be better than an implant, especially if the C.I. was high. Smears were examined until the 18th to 20th week of pregnancy to ensure that the placenta was taking over progesterone production. As regards late abortion, a more common complication than generally appreciated, the pregnancy might still be saved where the smear showed progesterone lack. Inadequate progesterone production was more common in infertility, habitual death of the fœtus, habitual premature labour, essential hypertension, and recurrent toxæmia; these cases should be watched weekly by vaginal smear. A persistently high C.I. was a bad prognostic sign and early hormone therapy could complement the lack and might save the pregnancy. Toxæmia of pregnancy with its variable placental pathology had tended to give inconsistent smears, but with the condition under control, as long as the C.I. was satisfactory and the smear, with its cell morphology and clumping typically progestational, the fœtus did not seem to be at risk. The C.I. in intrauterine fœtal death not associated with toxæmia of pregnancy was normal – presumably on account of the failure of œstriol synthesis. In cases of Rh incompatibility with a severely affected fœtus the C.I. was normal. In Behçet's syndrome there was a moderate rise in the C.I. throughout the pregnancy suggestive of a basic progesterone lack in this condition. Periodic high doses of this drug since pregnancy, in one case, seemed to have controlled the condition. [Graphs were shown of the C.I. in various pregnancy complications.]

It could be stated that vaginal cytology had an essential place in the routine tests of an antenatal clinic. It had diagnostic and prognostic values and was an immediate and reliable guide to hormone activity and the need for treatment. It was easy to perform and without risk to the patient.

REFERENCE
Spira H & MacRae D J (1960) *J. Obstet. Gynæc. Brit.Emp.* **67**, 597

Dr D F Hawkins (*London*) said that the discussion had so far been largely concerned with the exterior of the cervix. The major part of the vaginal portion of the human cervix consisted of a dense collagenous matrix in which lay isolated strands of smooth muscle. This intrinsic muscle of the cervix looked immature on staining and appeared to be practically incapable of movement by reason of the collagen in which it was enmeshed (Hughesdon 1952, Danforth 1954). The intrinsic muscles underwent hypertrophy and hyperplasia in pregnancy.

Dr Hawkins said that, though these fibres might not be capable of shortening much, they still might be able to exert tension. When a fresh specimen of cervix became available from a woman 10 weeks pregnant the reactions of isolated circular and longitudinal strips cut from sites representative of the intrinsic muscle were

studied isometrically, i.e. the force which they could develop was measured under conditions where no appreciable amount of shortening was required. When the preparations were maintained in Krebs-Henseleit solution at 37°C, at a resting tension of between 5 and 8 g/sq.cm cross-section, rhythmic contractions at frequencies between 1 and 4 per minute with amplitudes between 5 and 10 g/sq.cm were seen. These resembled the isometric contractions described as occurring spontaneously in the pregnant uterus *in vivo* by Alvarez & Caldeyro (1950). The maximum force developed spontaneously by these preparations was 18 g/sq.cm.

Responses of circular and longitudinal strips to drugs added to the medium in which they were suspended did not differ qualitatively. Adrenaline or noradrenaline (0·1–1·0 μg/ml), ergometrine (2–10 μg/ml), oxytocin (1–3 milliunits/ml) or histamine (1–10 μg/ml) elevated the tonus level. Papaverine (10 μg/ml) inhibited contractions previously stimulated by oxytocin or histamine.

The specimen had been provided by Professor Duncan E Reid and the experiments performed in the Department of Pharmacology at Harvard Medical School.

REFERENCES
Alvarez H & Caldeyro R
(1950) *Surg. Gynec. Obstet.* **91**, 1
Danforth D N
(1954) *Amer. J. Obstet. Gynec.* **68**, 1261
Hughesdon P E
(1952) *J. Obstet. Gynæc., Brit. Emp.* **59**, 763

Mr Bruce Eton (*Cambridge*) said that the colpomicroscope, invented by Antoine and Grünberger in 1949, permitted microscopic examination of the superficial cells of the portio vaginalis *in situ* in the living. It allowed accurate histological diagnosis of any changes which were detected and made it possible to keep a suspicious cervix under observation during and after pregnancy. Colpomicroscopy was also used in the search for the early stages of carcinoma of the cervix (Figs 1 & 2).

Mr Eton also made a plea for the abolition of the misnomer 'erosion'.

REFERENCE
Antoine T & Grünberger V (1949) *Klin. Med.* **4**, 15, 575

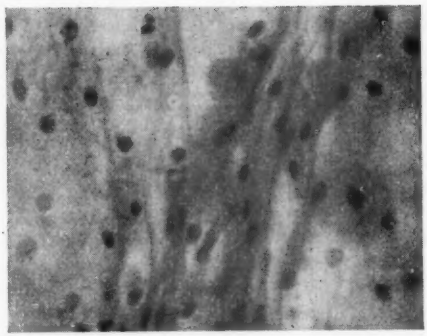

Fig 1 *Colpomicroscopy. Normal superficial squamous epithelium of the cervix*

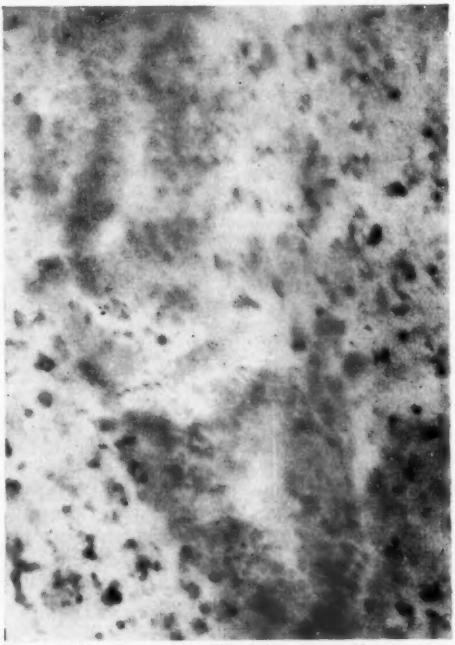

Fig 2 *Colpomicroscopy. Glandular ectopy showing two glands opening in a field of squamous epithelium*

Dr P C Sen Gupta (*Gloucester*) also took part in the discussion.

Book reviews

Infectious Diseases of Children
by Saul Krugman MD & Robert Ward MD
2nd ed pp 398 illustrated 97s 6d
St Louis: The C V Mosby Company
London: Henry Kimpton 1960

This is as admirable an account of infectious disease in childhood as would be expected of the two authors, both distinguished pædiatricians. Each chapter is devoted to a different disease which is described in detail, with considerable attention to the ætiological and pathological aspects. In spite of this the writing is clear and concise and it is easy to pick out any special points which may be needed for reference. In fact, it is so well written that it is a pleasure to read.

The references are as up to date as is possible in a textbook, and the sections on therapy are cautious and wise and give a balanced account of the use of modern remedies. No claims are made for any form of treatment that are not well substantiated.

The illustrations and diagrams are clear and helpful. The general format gives a good impression, the print is easy to read and the paper is of high quality. This should prove a valuable addition to the libraries of all who deal with infectious diseases in children.

Atlas of Human Anatomy
edited by Ferenc Kiss MD
and János Szentágothai MD
8th ed 3 vols £8 12s 6d
Budapest: Publishing House of the Hungarian Academy of Sciences—Publishing House Medicina[1] *1960*

This atlas which is edited by Professor Kiss, Professor of Anatomy in the University of Budapest, and Professor Szentágothai, Professor of Anatomy in the University of Pecs, and contributed to by Dr Munkasci, is in three volumes and has appeared for the first time in English. It has already been translated into Hungarian, German, Russian, Bulgarian and Chinese. The contents of the volumes are as follows:

Vol I – Osteology, syndesmology and myology.
Vol II – Splanchnology, endocrine glands and heart.
Vol III – Nervous system, vascular system, lymphatic system and sense organs.

The majority of the illustrations are in two or more colours, and have been drawn from original, specially prepared dissections. The drawings have been beautifully executed and annotated and give the student a realistic picture of the various anatomical structures. The production of these volumes must have been a formidable task, and the authors are to be congratulated for producing such a fine atlas.

[1]Also obtainable from Collet's Holdings, London,

A Primer of Space Medicine
by M P Lansberg MD
pp viii+165 illustrated 15s
Amsterdam &c: Elsevier Publishing Company 1960

Now that manned space-flight has finally been achieved, many doctors will be specifically interested in the physiological and psychological factors involved.

Dr Lansberg presents a review of these problems, with philosophical and mathematical undertones, but the text is uneven in its coverage. Less than three pages are devoted to the difficulties of re-entry into the earth's atmosphere, for example, yet this has been one of the chief problems which have delayed the achievement of manned orbital flight.

Nevertheless, all the important biological factors are at least mentioned, and a comprehensive list of references is provided so that the reader can himself pursue subjects which have aroused his special interest.

The Catarrhal Child
by John Fry MD FRCS
pp viii+139 illustrated 25s.
London: Butterworths 1961

Dr Fry is well known for his writing from general practice and his new book is an excellent documentation of ten years' experience as a family doctor in one of London's more salubrious suburbs. It gives a good account of the natural history of the only too common respiratory illnesses in children. Although a personal series, it is not greatly at variance with the other studies which have been undertaken. References in the text make this quite clear. These facts should be useful to those just going into general practice and not familiar with children, and help them to see the child with recurrent coughs and colds in true perspective. The book will also help to remind those working in hospitals that they see a highly selected group of these children and it leaves no doubt that, in some areas, the indications for tonsillectomy need reviewing.

Dr Fry shows that there is a peak incidence of all these respiratory infections occurring between the ages of 4 and 8 and depending on the child's contact with other children and sources of in-

fection, social conditions, and on his mother's ability to manage. After the age of 8 there is a dramatic fall in the occurrence of all the catarrhal child's symptoms. It is on this background that the effects of any treatment should be measured. In discussing the management of these cases Dr Fry pleads for a better understanding and liaison between doctor and family to prevent the mother losing confidence and becoming over anxious, rather than depending on a multitude of cough medicines, antibiotics and irrational removal of tonsils and adenoids. He shows the relative benignancy and perhaps inevitability of the respiratory illnesses, and the success of his conservative methods of treatment.

Modern Trends in Endocrinology (Second Series)
edited by H Gardiner-Hill MD FRCP
pp x+349 illustrated 75s
London: Butterworths 1961

The series of volumes entitled Modern Trends now needs no introduction as it has established for itself an excellent reputation for providing a good spectrum of up-to-date information concerning the expanding edge of specialized branches of medicine and surgery. A few of these volumes have now achieved second series and the present volume is one of these.

A very interesting collection of reviews is here gathered together and the standard of all of them is high, with excellent bibliographies. It is difficult to pick out individual chapters, but those on aldosteronism, thyroid auto-immunity and disorders of sexual differentiation are particularly good and of especial interest to most workers in the field of endocrinology at the present time.

The choice of subjects in this second volume on endocrinology is excellent as it complements in many ways the earlier volume in the series. It seems churlish to criticize, but it is a pity that the titles of papers are given in the references appended to some chapters but not in others. They are of real help as a guide to the literature and should be given with all the references.

Medical Evidence in Personal Injury Cases
by Dorothy Knight Dix QC and Alan H Todd MS BSC FRCS
pp xii+242 illustrated £2 2s
London: H K Lewis 1961

Books which relate medical and surgical practice to civil litigation and court procedure are rare, and the idea of joining the talents of two specialists in these fields must hold promise of new writing of great practical interest to doctors. As Lord Birkett says in his Foreword 'The great service this book renders is to define very clearly and in detail the rules by which the lawyer is governed, and the way the medical evidence can be concisely and clearly stated within these rules . . . '

Much the better contribution, if drily set out, comes from the law: the scope of medical evidence, legal aspects of examinations and report, the practitioner in the witness box and an evaluation of medical evidence, are adequately summarized for the doctor, and most heavily documented, as is the custom of the law. It is a pity some of Henry Cecil's wit or Glanville Williams smooth scholarship has not oiled the passage of the script, but it is all there so far as civil procedure needs are concerned. When we turn to the medical writing we must admit disappointment – in the main for its lack of balance. Apart from a short chapter on the C.N.S., and shorter essays on the genito-urinary tract and diabetes, half the text is 'civil litigation orthopædics', and had as much care been taken to explore other common grounds of litigation, this little guide to medico-legal procedure might have achieved a wide success. Lest we seem ungenerous, let it be made clear that this book sets out much that is of great practical interest to doctors engaged by lawyers to give evidence in County and High Courts: it is a reassuring guide for doctors who wish to understand and help in civil litigation problems.

A Syllabus of Laboratory Examinations in Clinical Diagnosis
edited by Lot B Page MD and Perry J Culver MD
2nd ed xxiv+580 illustrated 60s
Cambridge, Mass.: Harvard University Press
London: Oxford University Press 1960

This excellent book was originally written as a summary of a course given to second-year medical students at Harvard on the interpretation of laboratory examinations. The second edition contains thirty-four chapters, each written by one or more experts, describing the critical evaluation of tests done in a large teaching hospital in the investigation of patients. The range and scope of this book is wide, but the standard of presentation and of critical interpretation is remarkably uniform. There are no illustrations apart from graphs and occasional diagrams and the whole book is beautifully presented with good references which have been carefully chosen.

Bacteriology and pathology are intentionally omitted, but there are a few other omissions the reason for which it is difficult to understand. For example, no mention is made anywhere of tests for precipitins or antibodies in Hashimoto's thyroiditis, although these are now a part of regular laboratory practice.

This book is beautifully produced and not expensive. It is essentially a work of reference and could best find a place in the clinical laboratory where students work.